The natural history of chronic bronchitis and emphysema

AN EIGHT-YEAR STUDY OF EARLY CHRONIC OBSTRUCTIVE LUNG DISEASE IN WORKING MEN IN LONDON

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1 Background and the need for a prospective study

Summary

CHRONIC BRONCHITIS, or chronic non-specific lung disease, has been a major cause of fatal illness in Europe for at least two centuries, and nowadays affects all industrialized countries. There was little advance in the understanding of this complex of diseases until the last 25 years, when renewed interest arose in the United Kingdom. Clearer definitions of emphysema and of three categories of symptoms were agreed. Improved methods of diagnosis and treatment were developed by clinicians. Causation was investigated by epidemiologists from mortality statistics and by using new, standardized, methods in prevalence surveys. Heredity was thought to play a role of some importance but no widespread constitutional factors have been identified. Cigarette smoking was found to be the most important environmental factor operating at present, coupled with smaller but important contributions from air pollution, dusty occupations, and some unidentified influence of climate. Socio-economic status was found to have a major effect in the United Kingdom but apparently to have less effect in some other countries.

Before our study began, the natural history of the disease in its preclinical stages had been studied indirectly by retrospective clinical and pathological enquiry. Some research workers had postulated that the disease began with mucus hypersecretion and that this then predisposed to attacks of recurrent infection which could damage the lung and cause permanent airflow obstruction from bronchial narrowing and emphysema. Others thought that the airway narrowing and mucus hypersecretion were independent abnormalities in hyperreactive subjects and that infection was merely secondary. These two hypotheses have different implications for the prevention of disability.

In order to make direct observation of the early development of the disease, a prospective study was planned of the relationships of mucus hypersecretion, infection, and airflow obstruction with each other and with smoking habits in working men.

Historical background

Recognition of chronic bronchitis as a common and often gravely disabling disorder dates from the clinical accounts of the condition given by Badham (1808), who first used the word bronchitis, Laennec (1834), and Mackintosh (1831). During the rest of the nineteenth century many accounts of the symptoms and physical signs of the disease were published but there was little advance in diagnostic techniques, while therapeutic methods remained ineffective.

In the first half of the twentieth century little attention was given to bronchitis in medical research, although this disease remained a major cause of death, especially among the working classes. In 1923, Collis undertook a detailed review of mortality and morbidity statistics and commented,

> The trite observation that familiarity breeds contempt is essentially true with regard to the outlook on chronic bronchitis: those afflicted are inclined to accept the complaint as inevitable, as something troublesome but not serious. Those called upon to treat it do not find it sufficiently interesting to study closely. At a hospital it tends to be disregarded with an out-patient mixture yet ... records in England and Wales show that when mortality and morbidity are taken together, bronchitis is the most important of all diseases and further ... it is at the same time a most preventable disease.

Neglect of this common disease continued until 1951, when the Association of Physicians of Great Britain and Ireland held a symposium of chronic bronchitis. In 1953, Oswald *et al.* published an account of the clinical features of 1000 cases and Goodman *et al.* (1953), impressed by the predominance of chronic bronchitis as a cause of severe disablement, reviewed the data on mortality and morbidity. They drew attention to the large excesses of mortality among males, in the lower social classes, in urban areas, and in certain industrial occupations. They also emphasize the contrast between high British mortality rates and low rates in Scandinavia, which they thought might be due to contrasting levels of air pollution. Although the mortality rates are lower in Scandinavia than in Britain, chronic obstructive lung disease is still a major cause of death in every industrialized country.

A severe smog provided the impetus for renewed interest in research into the disease. Between 5 and 9 December 1952, a dense, cold fog hung over the city of London. Within one week there were 4000 extra deaths, which occurred, for the most part, in people already suffering from chronic respiratory or cardiovascular disease. In 1953 the British Medical Research Council set up a committee to advise on research into chronic bronchitis, which has

continued to encourage and integrate research into many aspects of the disease.

Definitions

When the members of the Medical Research Council committee first met, they found they were unable to agree on the definition or diagnosis of chronic bronchitis, especially in its earlier stages for, at that time, 'all but the later stages of the morbid process of chronic bronchitis were poorly understood' (Stuart-Harris and Hanley 1957). But even in the later stages there was considerable confusion between the diagnosis of chronic bronchitis and emphysema. Emphysema was assumed to be present in any patient with severe persistent airflow obstruction (Postgraduate Medical School 1951), but such patients were generally referred to as having 'advanced chronic bronchitis', often without any reference to the emphysema. In the USA, by contrast, such patients were almost invariably described as having emphysema with no reference to chronic bronchitis.

In 1959, a group of British workers (Ciba Guest Symposium 1959) proposed that diagnostic confusion could be reduced by defining emphysema on the anatomical basis—made possible by improved diagnostic techniques (Gough and Wentworth 1949)—of enlargement of the size of air spaces in the lung beyond the terminal bronchioles. (It was subsequently accepted (World Health Organisation 1961) that emphysema indicated enlargement of air spaces with destructive changes in their walls.) The workers that attended the symposium proposed that chronic bronchitis should be defined on a clinical basis in terms of chronic expectoration as first suggested by Scadding (1952), and asthma on the functional basis of reversibility of airflow obstruction. The general term 'chronic non-specific lung disease' was proposed as a term to cover all three conditions but was not recommended for general use lest this should inhibit attempts to distinguish between them. The term 'generalized obstructive lung disease' was suggested for irreversible airflow obstruction whether due to bronchitis or to emphysema, but this term has been superseded, especially in the USA, by 'chronic obstructive pulmonary, lung, or airways disease' (COPD, COLD, or COAD).

Although the proposals made at the Ciba Symposium gained wide acceptance, some confusion remained. The term 'chronic bronchitis' continued to be used without qualification to indicate, at one extreme, regular production of small quantities of sputum without any abnormality of lung function and, at the other extreme, severe airflow obstruction. The use of a single term to cover such

a wide range of abnormalities was justified by the hypothesis that they embraced the natural course of a single disease and that it was important for preventive purposes to identify potentially serious bronchitis at what was regarded as its earliest stage, a mere productive cough (Fletcher *et al.* 1959; Mitchell 1969). This 'unified' hypothesis is not one which is supported by the findings of our present study.

The concept of a single disease was reinforced by a report from the Medical Research Council's committee on research into chronic bronchitis (1965), which proposed that it should be classified into three stages—simple, mucopurulent, and obstructive. This report led some people to the additional idea, which was not intended, that airflow obstruction in 'obstructive bronchitis' must be due to obstruction of the airways by mucus gland hypertrophy and by intraluminal mucus (Thurlbeck *et al.* 1970). Consequently, the term 'chronic bronchitis' has unfortunately continued to be used to describe, without qualification, children with no more than a productive cough and patients gravely disabled by or dying from severe airflow obstruction. Despite this continuing semantic uncertainty, considerable advances have been made in relation to pathogenesis, pathology, and functional disturbances.

Bacteriology

Bacteriologists found that recurrent infections in the bronchi are associated predominantly with *Haemophilus influenzae* and *Streptococcus pneumoniae* (May 1972; Stuart-Harris 1968; Tager and Speizer 1975) and that viral or mycoplasmal infections are often initiating factors for these episodes of bacterial proliferation (Fisher *et al.* 1969; Cherry *et al.* 1971).

Physiology

Physiologists have devised simple tests for assessing the severity of airflow obstruction by measuring reduction of maximum expiratory airflow (Tiffeneau *et al.* 1949; Gaensler 1951; Wright and McKerrow 1959; McKerrow *et al.* 1960). In patients with severe airflow obstruction the pattern of disturbed function due to obstructive bronchitis (i.e. what might nowadays be called 'small airways disease') differed from that in emphysema (Ogilvie 1959; Fletcher *et al.* 1963; Nash *et al.* 1965; Burrows *et al.* 1966; Mitchell *et al.* 1970).

More specific techniques have now made it possible to distinguish the type of obstruction due to disease of the airways from that due to emphysema (Leaver *et al.* 1974). It has also come to be recognized that obstructive bronchitis and emphysema do not cause appreciable impairment of maximal expiratory flow until extensive disease has already developed. At autopsy it has been reported that estimated forced expiratory volume in one second (FEV) is not greatly affected until 25 per cent of the lung has been destroyed (Pratt *et al.* 1965). This is because in normal lungs 90 per cent of total resistance to airflow (the determinant of tests such as the FEV) is located in large airways, so a tenfold increase of resistance to flow in small airways is required to double the total airways resistance (Macklem and Mead 1967; Hogg *et al.* 1968).

A number of tests that may be capable of detecting lesser degrees of disease of the small airways have now been developed, and it has been suggested that these tests might be used to detect those smokers who will later develop disabling, irreversible airflow obstruction so that, if they could be persuaded to stop smoking, they might not develop severe disease (Macklem 1972).

Pathology

Pathologists have developed techniques for reproducible assessment of the severity of emphysema (Medical Research Council 1975) which have facilitated a number of studies of its prevalence and pathogenesis. Recognition of other widespread pathological changes in the peripheral airways of subjects with irreversible airflow obstruction is more recent. In patients with airflow obstruction, extensive narrowing, obliteration, and mucus plugging have been described (Hogg *et al.* 1968; Depierre *et al.* 1972; Matsuba and Thurlbeck 1973). These changes were taken to indicate 'small airways disease' and were generally described as 'inflammatory'. Although inflammatory changes are not always due to infection, this observation suggested that infection was causative.

Epidemiology

Epidemiologists have made studies of the prevalence and correlates of mucus hypersecretion, chest illnesses, airflow obstruction, and death rates from chronic respiratory disease in many countries. Many reviews of the results of these studies have been published (Stuart-Harris 1968; Van der Lende 1969; Gilson 1970; Higgins 1971; Reid and Fletcher 1971; United States Public Health Service 1971; Bennett *et al.* 1972; Fletcher 1973; Higgins 1974).

The broad aetiological conclusions which may be derived from all these studies are that cigarette smoking is now the most important cause of chronic obstructive lung disease, with air pollution and

occupational exposure to dust fumes also making a contribution, especially in cigarette smokers. The effect of geographical differences in climate is uncertain. The degree of damage caused by a given exposure is very variable, and only a minority of smokers develop severe obstruction. Little is known about the constitutional basis for this susceptibility but there does appear to be some inherited element. That other unidentified aetiological factors are also concerned is shown by the wide prevalence of, and high mortality from, what was diagnosed as 'chronic bronchitis' in Britain long before cigarette smoking became a common habit (Collis 1923) and by the largely unexplained social-class gradient of this which still exists, particularly in Britain, and which is not just due to differences in smoking habits.

The need for clarification of the natural history of chronic obstructive lung disease

When we planned our study, the concept was widely held that simple, mucopurulent, and obstructive chronic bronchitis were stages in a single process, which was often accompanied by the development of emphysema. This was based not only on the histories reported by patients, but also on the close associations found in many prevalence surveys between the chief manifestations of this 'process'—mucus hypersecretion, recurrent infection, and irreversible airflow obstruction. Subjects with persistent cough and sputum had, on average, a higher frequency of chest illnesses and lower ventilatory capacity than those without these symptoms (Fletcher *et al.* 1959; Sharp *et al.* 1965; Van der Lende 1969; Monto *et al.* 1975), but it had not been possible to determine whether this association was due merely to these conditions having common causes, or whether they were causally related to each other.

Retrospective epidemiological and clinical studies had emphasized the long course of the disease in many cases. Reid and Fairbairn (1958), Oswald *et al.* (1953), and Stuart-Harris and Hanley (1957), in clinical studies, had described the many years of chronic cough and recurrent illnesses which usually precede the development of disabling breathlessness. In many of their patients, however, the onset appeared to have followed an illness described as acute bronchitis or pneumonia; it was therefore suggested that the infection was a cause of lung damage leading to impaired ventilatory capacity. Stuart-Harris (1954) considered that infection was also a cause of chronic mucus hypersecretion rather than the reverse. Pathologists reported topographical associations between mucus gland hyperplasia, evidence of chronic inflammation (often assumed to be due to infection), and emphysema (Spain and Kaufman 1953; Reid 1954; McLean 1957; Leopold and Gough 1957; Reid 1965; Heard 1969). These were taken to indicate causal relationships.

'British' hypothesis

The hypothesis was consequently developed that in most cases the first stage in the development of chronic bronchitis was mucus hypersecretion, due predominantly to cigarette smoking but with general air pollution and respiratory infections also acting as contributory causes; that this hypersecretion impaired the defence of the bronchial tree to infection; and that infection produced disseminated bronchiolar obstruction and emphysema. Swabs taken at bronchoscopy confirmed that while the normal bronchial mucosa is sterile, pathogenic bacteria may be recovered from patients with persistent expectoration even when the secretion is mucoid (Lees and McNaught 1959; Laurenzi *et al* 1961).

If the hypothesis that airflow obstruction, due to bronchial narrowing or emphysema, resulted from injury due to acute or chronic bronchial infections were true, there would be important practical consequences, for it would imply that only those cigarette smokers who developed a productive cough would be liable to recurrent infections and thus at special risk of developing disabling breathlessness. This progression could perhaps be prevented by stopping smoking or, if stopping were not possible, it might be prevented by appropriate use of antibacterial drugs to control infection. Abrupt development of disabling airflow obstruction from an acute infection in previously healthy individuals might also be preventable by prompt use of chemotherapy.

This 'British' hypothesis was based entirely on retrospective reconstruction of events without any actual observation of the course of the disease. How misleading such reconstruction can be is shown by the patient described in Chart F.1 in the Appendixes. Moreover, there was some conflicting evidence at the time: patients sometimes developed severe emphysema without any preceding productive cough or history of infection (Mitchell and Filley 1964) and although ventilatory capacity was generally reduced during acute exacerbations of bronchial infection, it usually had been found to return, on recovery, to its previous level (Felix-Davis and Westlake 1956). Several studies have subsequently shown little relationship between exacerbations of clinically apparent infections, or their treatment, and deterioration of lung function (Medical Research Council 1966*b*; Howard 1974; Gregg 1969).

'Dutch' hypothesis

A different concept of the natural history of chronic bronchitis and emphysema was proposed, particularly by Dutch investigators. They suggested that chronic bronchitis and emphysema were closely related to asthma. In their view, airways narrowing developed as a primary abnormality in subjects who were over-reactive, in a manner analogous to allergic asthma, to a variety of allergic and other environmental stimulants (Orie *et al.* 1961; Van der Lende 1969; Orie and Van der Lende, personal communications). Bacterial infections were regarded as secondary to the primary obstructive condition, and possibly preventable merely by bronchodilator therapy or avoidance of allergens. The mechanism of the over-reactivity was considered to be complex but to include bronchial muscle contraction, mucosal swelling, and mucus hypersecretion. No clear mechanism was suggested whereby such changes could lead to irreversible obstructive changes. If this hypothesis were correct, a productive cough might be taken as an index of over-reactivity (although perhaps not as sensitive an index as a histamine test), but chemotherapy of infections would have little effect on the progression of the disease. When causative agents could not be avoided, treatment might be aimed at suppression of over-reactivity.

The present study

The most direct way to discover the actual course of events in obstructive lung disease is to observe their occurrence in a prospective study of subjects who have not yet developed disabling disease. The ideal of following a large population of both men and women from adolescence to old age was, of course, impracticable, but it seemed that useful information could be obtained from a relatively short-term study of British working men, with their high incidence of obstructive lung disease, during the ages at which clinical disease begins to declare itself. The number of men studied would have to be such as to make it probable that within the period of the study there might be significant differences between the mean changes in the extent of airflow obstruction in different subgroups. A population of subjects with a wide range of smoking habits, severity of mucus hypersecretion, and incidence of chest infections would be required to enable the interactions of these factors to be observed.

Because the population would have to be readily accessible and stable, men employed in local organizations with low manpower turnover were studied. Standard techniques of recording symptoms, of

sputum volume measurement, and of spirometry were thought to be sufficiently accurate and reproducible to provide useful results, and more elaborate or time-consuming techniques, although desirable, were not considered essential. In such a study, it was not possible to evaluate the effects of air pollution, climate, or occupation nor to make detailed studies of constitutional factors. The purpose was simply to discover the usual course by which disabling airflow obstruction developed, and some of the causes of its development.

In 1960, after an appropriate population of men had been found in West London (see Chapter 2), the Medical Research Council agreed, on the recommendation of its Committee on the Aetiology of Chronic Bronchitis, to support a study in which regular measurements would be made of sputum volume and of ventilatory capacity, and records would be kept of chest colds and chest illnesses and sputum purulence for a period of five years. In the event, the duration of the study was prolonged to eight years.

The study was designed to explore the interrelationships in time of the three main components of the bronchitis syndrome, to discover whether a chain of causation could be established, and to find out where in any such chain the well-established effect of smoking operated. The role of allergy was to be assessed by asking about personal and family histories of allergic conditions and by assessing sputum eosinophilia.

The study was not intended to investigate progression of the relatively severe airflow obstruction which is found in most patients who seek medical aid. Although men who had already reached this stage would not be excluded, *the main purpose was to delineate the earlier stages of the disease in men who were healthy enough to be in full-time employment*.

2 Methods

Summary

IN WEST LONDON, management and men working in an engineering works and in an office block agreed to co-operate with the study. A preliminary survey of these men, aged 30–59, showed a high enough prevalence of chronic phlegm production, recurrent chest illnesses, and impaired ventilatory capacity for a valid study of their inter-relationships to be practicable.

In 1961, a sample of 1136 of these men was drawn for follow-up. The sample was weighted to increase the proportion of men with bronchitic symptoms and of non-smokers. Twenty-five of the men were later excluded because of chest conditions other than airflow obstruction, and 319 men (including 90 who died) were excluded because they attended too few surveys. This report is mainly concerned with the remaining 792 men, whom we call the Follow-Up Group.

Surveys were carried out in the summer of 1961 and thereafter at six-monthly intervals until summer 1969, with the exception of winter 1966–7. Airflow obstruction was assessed by three measurements of forced expiratory volume in one second (FEV) at each survey (and two of vital capacity (VC) at seven surveys). After correction for observer and seasonal biases, the rate of change of FEV was estimated as the regression of FEV on time minus 15 ml/year. Bronchial infection was assessed by recording chest illnesses and colds which had occurred in the intervals between surveys and by assessing the purulence of the sputum specimens. Mucus hypersecretion was assessed by measurement of early morning sputum volume and by questions at the summer surveys about chronic phlegm production. Current smoking habits were recorded at each summer survey.

In addition, various special studies were undertaken at particular surveys. Lifetime smoking habits were recorded in 1965. Allergy was assessed by questions on personal history of asthma and hay fever in 1961, by a detailed allergy questionnaire in 1965, and by the presence of eosinophils in the sputum specimens at three of the surveys. Chest X-rays were taken of men attending in 1967. A questionnaire on childhood illnesses was completed in 1965 and

measurements of skinfold thickness on the back of the hand were made at the same time. Serum antibodies to *H. Influenzae* were determined in 1968. Although some use was made of these additional measurements, the main point of the study was our regular assessment, over an eight-year period, of FEV, expectoration, smoking, and symptomatic chest infections in 792 middle-aged men.

Choice of population

A stable and co-operative male working population suitable for the proposed study was sought by visiting a number of factories and offices in West London in 1958. The London Transport Workshops at Acton and Chiswick, concerned at Acton with the maintenance of railway stock and at Chiswick with maintenance of buses, employed approximately 4000 men and had the remarkably low labour turnover during the previous 10 years of some 1 per cent per year. A further population, about half as large and of similar stability, was found at the Post Office Savings Bank at Hammersmith.

At the London Transport Workshops the men worked in large sheds at ground level, which were frequently opened to admit vehicles. These sheds conformed to Factory Act requirements that the temperature must reach 16 °C within one hour of starting work. The majority of men working there were skilled machine operators or foremen of Social Class III (manual). Some of these were later promoted to supervisory grades. There were also a few unskilled workers. Their earnings in 1961 ranged between £800 and £1200 per annum. The official working week was 44 hours. It was shortened to 42 hours in 1960 and to 40 hours in 1965, with occasional overtime.

The Post Office Savings Bank was housed in a large Victorian block of offices with central heating. The temperature was maintained close to 22 °C. Most of these men were clerical officers of Social Class III (non-manual), with earnings similar to those at the London Transport Workshops. At the Post Office Savings Bank there was a 40-hour, five-day week, with frequent overtime.

Representatives of management and men were approached about the possibility of carrying out a prospective study of bronchitis and heart disease, which would probably continue for at least five years, and willing co-operation was assured. It was explained that a preliminary survey would be needed to establish whether the prevalence of bronchitic symptoms was sufficient to justify embarking on a long-term follow-up study. The study eventually continued for eight years, 1961–9.

Preliminary surveys

The prevalence of dyspnoea and chronic phlegm production was estimated by issuing a short, self-administered questionnaire (Appendixes, Section A.1) to all the men in February 1959. Analysis of the replies showed that, after adjustment for smoking habits, the prevalence of symptoms was similar at the London Transport Workshops and at the Post Office Savings Bank.

A 1 in 5 random sample of men aged 30–59 at the London Transport Workshops was studied more fully in March 1959 by interview, sputum collection, and measurement of peak expiratory flow rate. The questionnaires used and results obtained have already been published (Fletcher and Tinker 1961). The age limits were chosen because men over 59 would be likely to retire before the end of a prolonged follow-up study, and few men under 30 were thought likely to develop significant airflow obstruction in this period.

Our study has led us to believe that the development of impaired ventilatory capacity is usually a gradual process, without any abrupt transition from 'normal' to 'abnormal'. Because of this, the duration and size of future prospective studies of the relationship of the rate of development of impairment to various factors should be selected in the light of the accuracy with which differences between rates of change will be estimated. (In section B.10 of the Appendixes, reasons for preferring a minimum of seven years follow-up for the study of rates of change of FEV are given.) Although our prospective study data have now been interpreted in terms of gradual changes over eight years, the sample size and study design were originally selected for the detection of attack rates.

On the basis of the 1959 prevalence survey (Table 2.1), it was estimated that 5000 man-years of observation of a random sample of the London Transport Workshops work-force would yield 95 onsets of 'chronic mucus hypersecretion' and 45 onsets of 'significant ventilatory impairment', defined as in Table 2.1, plus 400 chest illnesses and 1500 chest colds. This was felt to be sufficient for some meaningful inferences about the interrelationships of these conditions to be possible, and on this basis a sample of over 1000 men to be followed for at least five years was sought. In the event, well over 5000 man-years of follow-up were obtained, but the definitions in *Table 2.1 were not in fact used in the analysis of the follow-up data.*

Selection of a stratified sample

Further discussions were held with management and representatives of the men in 1960. It was explained that the follow-up study would

Table 2.1. 1959 pilot survey

Results of the 1959 pilot survey at the London Transport Workshops: percentages with various conditions by age group

Condition	Age 30–39 (76 men)	Age 40–49 (112 men)	Age 50–59 (195 men)	Apparent annual increase† in percentage with this condition	
				35–45	45–55
Percentage with chronic mucus hypersecretion‡	24	28	43	+0·4 per year	+1·5 per year
Percentage with significant ventilatory impairment§	7·9	7·1	12·8	−0·08 per year	+0·37 per year

† Assuming differences in prevalence to be due solely to an attack rate with advancing age.
‡ Phlegm production on most days for at least 3 months per year and/or 2 ml or more of morning phlegm.
§ Peak expiratory flow more than 2 S.D. below the mean of men of the same age and height without dyspnoea or chronic phlegm.

Table 2.2. The 1961 sampling scheme

Numbers of men aged 30–59 selected for interview and numbers included in initial survey, 1961

Sample group	Intended sampling fraction (per cent)	London Transport Workshops						Total			Inclusions as percentages of those available
		No. available	No. selected	No. included	Inclusions as percentage of those selected	No. available	No. selected	No. included	Inclusions as percentage of those selected	Inclusions as percentage of those available	
Group 1 (Symptomatic)	100	430	430	415	96·5	222	222	211	95·0	652	96·0
Group 2 (Asymptomatic non-smokers)	50	189	94	89	94·7	93	47	45	95·7	282	47·5
Group 3 (Asymptomatic smokers or ex-smokers)	20	796	155	151	97·4	437	84	80	95·2	1233	18·7
Group 4 (No questionnaire returned)	30	760	214	145	67·8	86	0	0		846	17·1
Total	*41*	*2175*	*893*	*800*	*89·6*	*838*	*353*	*336*	*95·2*	*3013*	*37·7*

be carried out on only a proportion of the men, and that few of the selected men would derive any benefit from the study, the sole purpose of which would be to increase knowledge about common disabling diseases. Findings on individuals were to be confidential. It was, however, agreed that if any abnormality needing treatment was detected, the man would be informed and his permission obtained to write to his own doctor, whom he should then consult. At both places, representatives of the men welcomed the proposals and the management agreed to allow men to leave their work for interviews and measurements without loss of earnings. At the London Transport Workshops the cost of men leaving their work was to be reimbursed; at the Post Office Savings Bank no charge was to be made. The management supplied lists of names, dates of birth, and works numbers: members of the staff agreed to distribute the preliminary questionnaires and to work out appointment lists for six-monthly surveys.

At the end of 1960, 3013 men aged 30–59 were available, including both salaried and wage-earning staff at the Post Office Savings Bank but only wage-earning staff at the London Transport Workshops. To draw a sample of approximately 1000 men, stratified according to their symptoms and smoking habits, another self-administered questionnaire (Appendixes, section A.2) was distributed to all the men by the managements in March 1961. The sampling scheme was designed to include all men with symptoms of respiratory disease, to increase the proportion of non-smokers (to act as controls for the more numerous smokers), and to take a smaller proportion of the many smokers without evidence of chronic phlegm production.†

To this end, the men were put into four groups according to their replies to the questionnaire, as follows (Table 2.2):

GROUP 1: 'Symptomatic men' who admitted to chronic phlegm production ('Yes' to question 4) or to recent chest illnesses ('Yes' to question 7 or 8) and men who were on sick leave on account of an illness certified as respiratory in nature by their general practitioners. All the men in this group were selected.

GROUP 2: Men who denied having ever smoked regularly (Part II of the questionnaire) who had not been included in Group 1, and were thus 'asymptomatic non-smokers' ('No' to questions 4, 7, and 8). Half of these men were selected.

GROUP 3: Men not included in groups 1 or 2 who were thus 'asymptomatic smokers or ex-smokers'. One in five of these men was selected.

GROUP 4: Men who did not return the questionnaire, a few because of a temporary illness. At the London Transport Workshops 30 per cent of these men were selected. At the Post Office Savings Bank the questionnaires were distributed and collected by an officer of the staff association and 89 per cent of the questionnaires were returned. The remaining 11 per cent of the men were unwilling to take part in the study and, at the request of the staff association, no further approach was made to these men. Thus, there were no group 4 men from the Post Office Savings Bank.

† This sampling scheme was designed by Dr. A. S. Fairbairn, then a member of the Medical Research Council's Statistical Research Unit.

Men in these four groups were asked to attend the initial survey, and at both the London Transport Workshops and the Post Office Savings Bank 96 per cent of the men in groups 1, 2, and 3 did so. Only two-thirds of the men in group 4 attended. The 1136 men who attended the initial survey (Table 2.2) are referred to as the *stratified sample*. From the sampling fractions and the proportion of men in each of the sample groups, it can be estimated that 2601 men of the total population would have been willing to attend the survey if asked and 412 men would have refused. These 2601 men (86 per cent of all available men) are referred to as the *total co-operative population*. The prevalence of symptoms and levels of various measurements in this population are estimated from the prevalence and levels observed in the stratified sample, taking account of the sampling fractions (see below).

Since the stratification scheme adopted was biased against asymptomatic smokers, it distorted the relationship between smoking and symptoms that would have been found in a purely random sample. Although a distortion such as this can always be allowed for (Appendixes, section B.7), such allowance means that all random errors are larger than they should be, and all tabulations and regressions are slightly more complicated to calculate and describe than they would have been if no such allowances were necessary. Stratification based on two factors is not desirable in such studies, and it would have been better if we had merely stratified with respect to smoking (selecting all the non- and ex-cigarette smokers plus about a third of the current cigarette smokers), since our subsequent tabulations and regressions would then not have needed adjustment for the selective nature of the initial sample.

Procedures at the initial survey, 1961

Arrangements were made for the men in the stratified sample to be interviewed and examined at the places where they worked. The survey started in April and ended at the beginning of August 1961. The questionnaire used (Appendixes, section A.3) was a slightly modified version of the Medical Research Council's (1966*a*) Questionnaire on Respiratory Symptoms.

Each man was received by a clerk, who weighed him without coat and shoes and measured his standing and sitting height. The

man was then randomly allocated to one of two interviewers, who completed the questionnaire. The interviewers were State Registered Nurses who had been trained in the technique of interviewing with a standard questionnaire. The first hundred interviews were monitored by tape-recordings and one or two minor discrepancies in techniques were corrected.

Five acceptable readings were then made in the sitting position of the forced expiratory volume in one second standardized to body temperature (FEV), using a Poulton spirometer (McKerrow *et al.* 1960). The nearest 50 ml mark on the dial *below* the needle was taken as the correct reading. The readings of blood-pressure and FEV were made by one of three doctors, to whom the patients were allocated in order of attendance.

During the initial survey at the Post Office Savings Bank, measurements of FEV were repeated after an interval of 8–11 days on a random sample of 152 of the 336 men who attended. The mean value was 3·227 litres on the first and 3·243 litres on the second occasion. Eighty-one per cent of the readings agreed within ±300 ml and 92 per cent within ±400 ml (Fletcher 1964). The mean readings of the three observers did not differ significantly.

The interviews and measurements were completed in about 30 minutes. Each man was then given a sterile 25 ml 'universal container' into which he was asked to expectorate all the phlegm brought up from his chest in the first hour after getting up on the morning of the day after the interview (on Monday in the case of interviews on Friday). The bottles were to be returned before noon in an envelope which was provided. The instructions were given verbally and by a note accompanying the sputum container (Elmes *et al.* 1959).

The sputum specimens were examined on the day of collection by a doctor or a senior technician, who recorded the volume by comparing each container with a row of identical bottles containing volumes of coloured water ranging from 1 ml to 20 ml. The volume of sputum was recorded to the nearest millilitre below the actual volume and 0·5 ml was added to all readings of non-empty bottles. A specimen of less than 1·0 ml was thus recorded as 0·5 ml; specimens of 1·0–2·0 ml were recorded as 1·5 ml, and so on. In the course of the survey, techniques for quantitative recording of sputum purulence and eosinophilia were developed (Miller and Jones 1963). They were used in some subsequent surveys, but neither of these indices was recorded at the initial survey.

Most of the men who attended the initial survey had been X-rayed recently by the local miniature radiography unit, which visited their

Table 2.3. Numbers of attendances at each survey 1961–9

Survey number	Year	Follow-Up Group	Lapses	All men
1	1961	792	344	1136
2	1961–2	758	263	1021
3	1962	742	241	983
4	1962–3	722	220	942
5	1963	727	225	952
6	1963–4	725	190	915
7	1964	717	172	889
8	1964–5	688	151	839
9	1965	690	131	821
10	1965–6	684	93	777
11	1966	714	98	812
12	No survey	—	—	—
13	1967	644	29	673
14	1967–8	701	23	724
15	1968	685	14	699
16	1968–9	676	15	691
17	1969	682	6	688
Average no. of surveys attended		14·3	6·4	11·9

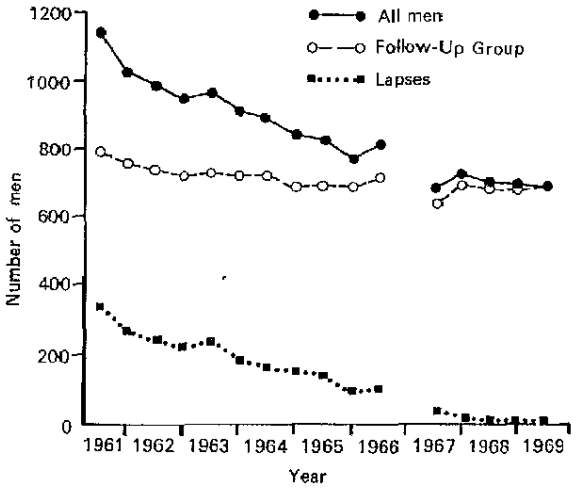


Fig. 2.1. Numbers of men attending each survey

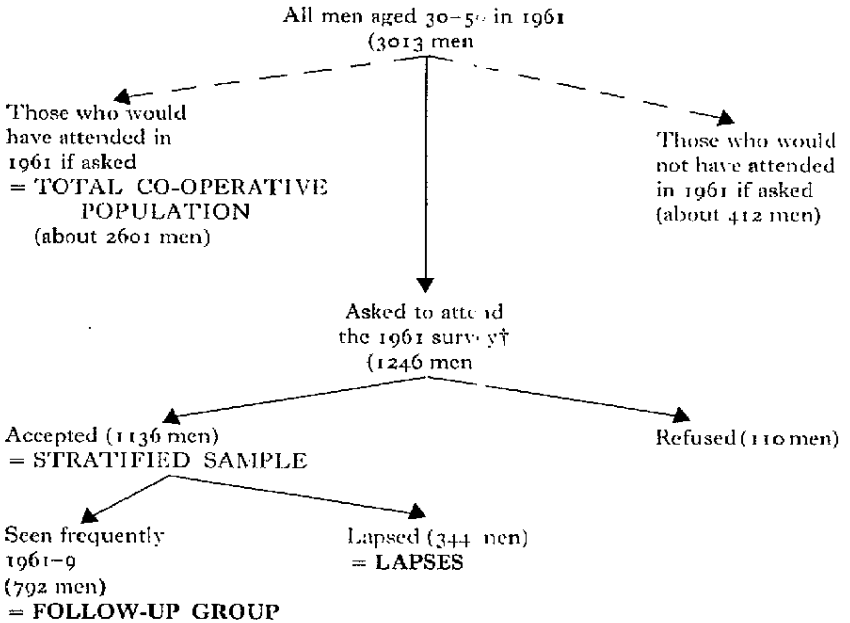
places of work every other year. Reports on these films were obtained and entered on the men's records. Reports were also obtained from chest clinics and hospitals where appropriate.

The Follow-Up Group†

In the course of the study there was a steady loss of men, greater than had been expected on the basis of the low manpower turnover recorded in preceding years, from the stratified sample examined at the initial survey (Table 2.3; Fig. 2.1). The diminution of the lapse rate in 1966 was due to special efforts which were made to continue observations on men who had stopped working at the London Transport Workshops or at the Post Office Savings Bank but whose whereabouts were still known. In the later years of the study, some 60 of these men continued to attend regularly at Hammersmith Hospital, and a further 30 were visited at their places of work or their homes in various parts of the country by health visitors. Men failed to continue to attend for a variety of reasons, the chief of which was that they were disappointed that the study was not providing them with medical advice; a few men happened to feel unwell after a survey and blamed one of the tests, and others just 'lost interest'. One hundred and eleven men transferred to other employment or retired prematurely early in the course of the study, and there were 90 deaths; the relevance of the initial survey findings to subsequent mortality will be reported elsewhere. Three men were excluded because they were receiving bronchodilator or steroid therapy for the greater part of the study, which precluded observation of the natural development of their airflow obstruction (see p. 20).

As a result of these losses, there were 319 men for whom insufficient acceptable measurements of FEV were available to provide reliable estimates of their regressions of FEV on time (Appendixes, section B.4). These men, together with 11 who had had a previous lung resection, 4 who developed lung cancer, 3 who had asthma requiring continuous therapy, and 7 other men (Appendixes, section B.4), 344 in all, are referred to as *Lapses*. The remaining 792 men, including 17 clinical asthmatics who were not receiving continuous therapy and some other possible asthmatics, comprise the *Follow-Up Group*. The derivation of this group from the total population of men available in 1961 is illustrated in Fig. 2.2.

† Previous reports on the first seven years of the study (Fletcher 1968; Fletcher *et al.* 1970, 1971) were made on a slightly different group of men: in particular, 32 men who gave a history of asthma were excluded. It was suggested by Orie (1970) that this exclusion could conceal any relationship of allergy with the development of airflow obstruction. For this reason, these men have been included in this final analysis except for 3 men rejected because they were receiving bronchodilator therapy.



† Invitations sent to approximately
100 per cent of symptomatic men
50 per cent of asymptomatic non-smokers
20 per cent of asymptomatic smokers
30 per cent of men not returning questionnaire.

Fig. 2.2. Derivation of men in Follow-Up Group

Procedures at follow-up surveys

The basic plan of the study was to make recordings every six months of ventilatory capacity, chest illnesses, and expectoration. In the summer, when sickness absence is less frequent, it was easier for the management to allow men to leave their work, and extra time could be allowed for additional studies. During the first two years, special methodological studies were also carried out on small samples of men. The study was originally planned for a period of five years but this period was extended by a further three years with omission

one winter survey (survey 12) to confirm the pattern of change of utum volume and FEV during the first five years and to increase e accuracy of assessment of the rate of decline of FEV in individuals id in groups of men. Table 2.3 shows the number of men in the ollow-Up Group attending each survey, and Table 2.4 shows the rveys at which the various routine and special measurements ere made.

leasurement of lung function

orced expiratory volume in one second (FEV). FEV was measured at ery survey by nurses and technicians by the same technique as as used at the initial survey. Ideally, these measurements should l have been made by the same observer, but this was impossible id 21 observers were used over the eight years of the study. They ere all carefully instructed in the technique. Before each new bserver's observations were accepted, he or she and an established bserver made independent duplicate recordings of FEV and obtained answers to the routine questionnaire on 40 subjects. The rder of measurements and interviews was randomized between the vo observers. The results were analysed immediately and any chnical errors thus disclosed were discussed with the new observer nd corrected. On no occasion did the mean readings of FEV by ie new and old observers differ by more than 80 ml, and seldom y more than 40 ml. (Our later estimates of 'observer biases' are ased on all the measurements that each observer made, not on the esults of these training sessions.)

The accuracy of the Poulton spirometers was checked each day y the calibrating device provided. The temperature of the water n the spirometer was maintained very carefully between 18 °C nd 22 °C, and FEV (BTPS) was read directly.

If the readings on any man were judged by the observer to be ffected by poor co-operation or by any temporary physical disbility (such as recent dental extraction or the wearing of a spinal acket), the fact was noted and the readings taken at that survey vere not used in the analysis. In the course of the study, 90 readings 0·7 per cent of all readings) on a total of 65 men were excluded or such reasons. The men were also asked at most summer surveys whether they were taking any treatment for difficulty in breathing.)ne or more readings from 19 men were excluded because of ronchodilator or steroid therapy at the time of a survey, and because *f this 3 of these 19 men were treated as Lapses only because they* vere under treatment for most of the study.

At each survey, five FEV readings were taken, two practice blows

Table 2.4. Procedures carried out at each survey, 1961–9

Number:	Survey 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Year:	1961	1962		1963		1964		1965		1966		1967		1968		1969	
Winter/summer:	S	W	S	W	S	W	S	W	S	W	S	W	S	W	S	W	S
Questionnaires																	
Phlegm	B	—	B	—	B	—	B	—	B	—	B	—	B	—	B	—	B
Chest illnesses	B	B	B	B	B	B	B	B	B	B	B	—	B	B	B	B	B
Childhood illnesses	—	—	—	—	(B)	—	—	—	—	—	—	—	B	—	—	—	—
Current smoking habits	B	—	B	—	B	—	B	—	B	—	B	—	B	—	B	—	B
Lifetime smoking habits	—	—	—	—	—	—	—	—	B	—	—	—	—	—	—	—	—
Cardiovascular symptoms	B	—	B	—	B	—	B	—	B	—	B	—	—	—	—	—	—
Allergy	—	—	—	—	—	—	—	—	—	P	—	—	L	—	—	—	—
Measurements																	
Sputum volume	B	B	B	B	B	B	B	B	B	B	B	—	B	B	B	B	B
Sputum purulence	—	B	B	B	B	B	B	B	B	B	B	—	B	B	B	B	B
Sputum cosinophilia	—	B	—	—	—	—	B	—	B	—	—	—	—	—	—	—	—
H. Influenzae antibodies	—	—	—	—	—	—	—	—	—	—	—	—	—	—	B	—	—
Standing height	B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Weight	B	—	B	—	B	—	B	—	B	—	B	—	B	—	B	—	B
FEV	B	B	B	B	B	B	B	B	B	B	B	—	B	B	B	B	B
VC	B	—	—	—	—	B	—	—	B	—	—	—	B	—	B	B	B
Airflow resistance —	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Scapular/triceps skinfold	B	—	(P)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hand skinfold	—	—	—	—	—	—	—	—	—	—	—	—	B	—	—	—	—
Allergen skin tests	—	—	—	—	—	—	—	—	—	—	(P)	—	—	—	—	—	—
Chest X-ray	—	—	—	—	—	—	—	—	—	—	—	—	B	—	—	—	—

B = at both the Post Office Savings Bank and the London Transport Workshops
P = at the Post Office Savings Bank only
L = at the London Transport Workshops only
Brackets indicate sample only

lowed by three recorded blows. For all the analyses the measured EV was taken to be the largest of these three recorded blows (see ppendixes, section B.1). All the measured FEV levels at each survey ere corrected for minor biases attributable to differences between servers or between seasons (see section B.2 of the Appendixes). ese corrections were typically of a few centilitres only: the most treme was the correction needed at survey 5 after the cold winter 1962–3, which was nearly 130 ml (Fig. 2.3). After applying these rrections, no seasonal fluctuations in the FEV remained. (The data Fig. 2.3 are given in Table 4.1, p. 55.)

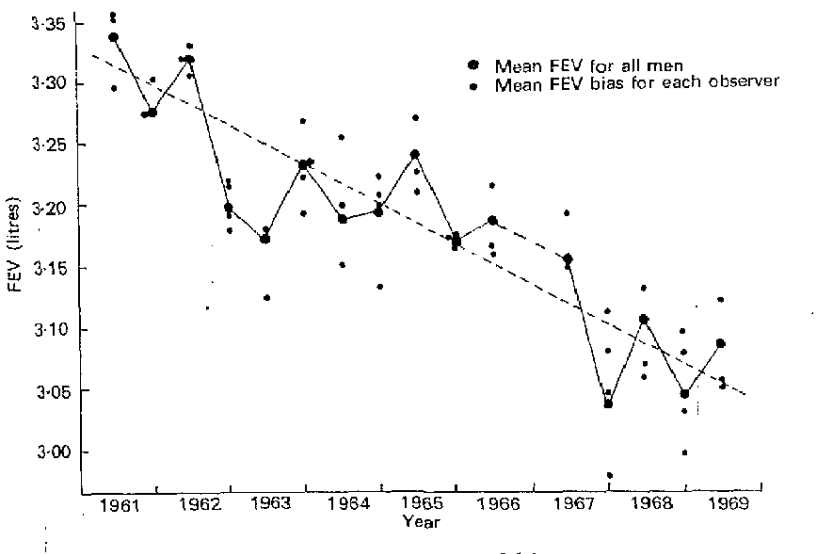


Fig. 2.3. FEV means and biases

an FEV survey by survey for 347 men who gave acceptable readings at every survey, l mean observer biases at each survey.

The mean annual rate of loss of FEV in the Follow-Up Group is 30 ml/year. In our analysis of the causes of FEV loss, we derived o main quantities from the FEV measurements for each man— s *mean FEV* and his *FEV slope*. His *mean FEV* is a weighted erage of all his corrected FEV measurements, standardized to 65 by 30 ml/year. (Most men in the Follow-Up Group had similar mbers of FEV readings before and after 1965, and so their mean EV is unaffected by their standardization.) The weights were ghtly larger for readings taken at later surveys because the men d learned to perform more accurately by then. This weighting of

the mean FEV was done to eliminate regression to or from the mean (Appendixes, sections B.5 and B.16).

If we take a man's mean FEV in 1965 and draw a line of slope 30 ml/year through it, it is unlikely that any of his corrected FEV measurements will be outliers which deviate by more than ±0·45 litres from this line. The *FEV slope* for that man is derived by omitting any such outliers, calculating the regression coefficient of the remaining measurements, and subtracting 15 ml/year from it. Most of the outlying values thus omitted seem to be data errors (Appendixes, section B.5; p. 124; Appendixes, Charts F. 15–18), and their exclusion ('winsorization') makes the trend in the remaining measurements more reliable. The 15 ml/year correction to each slope was introduced because we believe (Appendixes, section B.3; p. 125; Appendixes, Chart F.16) that poor FEV technique in the earlier surveys may have made the simple regression coefficients too shallow. A fuller description of how we treated our FEV measurements is given in sections B.1–B.5 of the Appendixes, with a summary of it in section B.5.

Vital capacity (VC) and the ratio FEV%VC. No measurements of VC were made in the first two years of the study because this measurement was then considered unreliable and unnecessary for assessment of lung function in epidemiological surveys. This omission was subsequently corrected and two measurements of slow VC were made on each man at the sixth survey in January 1964, at the ninth survey in July 1965, and at the thirteenth to seventeenth surveys, after the measurement of FEV. The mean of the two VCs at each of these surveys was recorded. (In retrospect, we would have slightly preferred to have used the larger of the two—see section B.6 of the Appendixes.) These means were then corrected (section B.2) for observer and seasonal biases, and the VC for each of the 792 men in the Follow-Up Group was defined as the maximum of the corrected mean VC values recorded for him. This maximal VC is henceforward referred to simply as the VC. The ratio 100 × (mean FEV)/VC was calculated and is referred to as FEV%VC. Insufficient readings of VC were obtained for a reliable estimate of VC slope.

Measurements of airflow resistance. In 1962 it was thought that an increase in airflow resistance on smoking a cigarette might be an indication that a man was likely to develop persistent airflow obstruction. Pilot measurements of airflow resistance by a body plethysmograph were therefore made on a small sample of men at the Post Office Savings Bank before and after smoking a cigarette

(McDermott and Collins 1965). Since an association was found between the change of resistance and bronchitic symptoms, these measurements were repeated at the ninth survey on 752 of the men who attended (Guyatt *et al.* 1967; Alpers and Guyatt 1967; Guyatt and Alpers 1968). It was found that the association previously observed was merely due to a greater change of resistance in men who inhaled more deeply during the test, because depth of inhalation during the test was correlated with daily cigarette consumption and this with more frequent bronchitic symptoms. After allowing for this, there was no remaining association with symptoms of bronchitis (Guyatt *et al.* 1970). We have included the 1965 data in our present analysis, confining our interest to men who were regular smokers (and hence accustomed to the effects of cigarette smoke). The increase in airflow resistance on smoking a cigarette was estimated as zero if the second resistance measurement was less than the first, and as the difference between the two resistance measurements otherwise.

Measurements of bronchial infection

Respiratory illnesses. The original plan was to collect information on all respiratory illnesses, however mild, which might affect ventilatory capacity. An attempt to do this was started in October 1961. Each man was sent a reply-paid postcard every two weeks on which he was asked to record whether he had suffered from a cold or any other sort of chest illness or had had a persistent increase in phlegm production during the preceding two weeks. So many men reported episodes that the accuracy of the replies could be checked in only a small proportion of them, and even in those checked it was difficult to know whether there had been one continuous or two separate episodes. This frequent recording of minor respiratory episodes was continued for only six weeks. Reliance was thereafter placed on reports of chest illnesses and chest colds given by the men at each six-monthly survey. Chest illnesses recorded at the initial survey referred to the previous three years and those at the second survey were recorded on a pilot questionnaire which was later modified. Only chest illnesses and chest colds recorded on the standard questionnaire (Appendixes, section A.4) used at the third (summer 1962) and all subsequent surveys are used for the correlations of these episodes with other measurements.

In the standard questionnaire each man was first asked about any chest illness which had kept him in hospital or bed for a week or more; subsequent questions were then asked about flu or chest colds and about associated increases of phlegm and changes in its colour. In a special study of chest episodes (Angel *et al.* 1965), the first of these

questions about a definite increase of phlegm with the episode was found to produce reliable answers, but the replies to the questions about the duration of the increase and about changes in the colour of sputum did not correspond well with what had been observed at the time of the episode. No use was therefore made of replies to these questions, nor of answers to the question on periods of increased cough and phlegm, since few were recorded by men who had not also recorded a chest illness or chest cold. Eighty per cent of these chest illnesses or chest colds were associated with an increase of phlegm, and only those with an increase were used in the multiple regression analysis (but see Appendixes, section B.8). For most purposes chest illnesses with phlegm and chest colds with phlegm were combined, and referred to as 'chest episodes'. (A preferable method of scoring these chest episodes, for use in future studies, is put forward in section B.8 of the Appendixes.) The frequency of chest episodes for each man is the number of surveys from summer 1962 to summer 1969 at which he reported an episode, expressed as a percentage of the number of these surveys which he attended. This method of recording slightly underestimates the frequency of all chest episodes, since a few men reported more than one chest episode at one survey. (The mean chest episode frequency in a particular *group* of men is calculated as the average of their percentage frequencies rather than as the total number of episodes reported divided by the total number of surveys attended by these men.)

One major difference between our technique of dividing chest episodes into severe ones (chest illness) and others (chest colds) and the technique used by other workers should be emphasized. The Questionnaire on Respiratory Symptoms (Medical Research Council 1966*a*) asks whether a week in bed *or off work* was involved. We asked this, too, in 1961 but at all the routine surveys from 1962 to 1969 we asked about a week in bed, and this is a more restrictive criterion.

Sputum purulence. The purulence of sputum specimens was graded at each follow-up survey by a technician trained in the method described by Miller and Jones (1963). There were four grades: M_1, pure mucoid; M_2, suspicion of pus; P_1, pus less one-third of the sputum; and P_2, pus one-third or more of the sputum. These were scored respectively 2, 3, 5, and 10 on the basis of polymorph counts in a sample of such sputum specimens (Miller and Jones 1963). The total score for each group of three specimens thus ranged from 6 to 30. When less than three specimens were returned by any man, the mean score multiplied by 3 was used. The distribution of

purulence scores in the 4117 sets of sputum bottles containing at least one sputum specimen over the years 1962–8 is shown in Fig. 2.4. The peaks at scores of 6, 9, 15, and 30 correspond to groups of

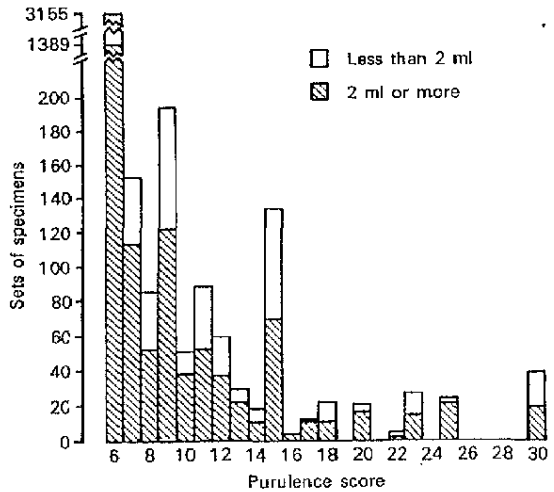


Fig. 2.4. Purulence distribution
Distribution of purulence scores in non-empty sets of sputum bottles 1961–8 (4117 sets).

specimens all with the same scores of 2 (M_1), 3 (M_2), 5 (P_1), or 10 (P_2). A set of sputum specimens at any one survey with a score of 9 or more (at least one P_1 specimen or three M_2 specimens) was considered 'purulent' and a set of specimens with a score of less than 9 was considered 'mucoid'. (For the reasons discussed in section B.8 of the Appendixes, it would have been slightly preferable to have grouped everything other than 'pure mucoid' together as 'purulent', but what was actually done was, if not absolutely optimal, at least valid.) Observer variation was small (Appendixes, section E.3, p. 233).

In the regression analyses the quantitative index of sputum purulence for each man was the proportion of all the follow-up surveys attended from summer 1962 onwards at which he returned a purulent specimen, thus defined. A qualitative index dividing men into those who never produced a purulent specimen and those who produced at least one purulent specimen was also used.

Haemophilus influenzae antibodies. The presence of these antibodies

was assessed at the fifteenth survey in 1968. The results have already been reported (May *et al.* 1973)

Measurements of expectoration

Sputum volume. At all the surveys after the initial one, each man was asked to provide three specimens of the sputum he produced during the first hour in the morning. This was done because it was found that the mean volume of three specimens collected on successive days provided a more accurate estimate of the mean volume of 10 specimens taken on successive days than did a single specimen, but that there was little increase in accuracy if more than three specimens were obtained (Miller *et al.* 1965). At surveys 2–5, specimens were obtained on successive days, but at subsequent surveys they were collected on the same day in three successive weeks. The volume of each specimen was measured as at the initial survey: the mean volume of each group of specimens was used for the analysis.

Indices of sputum volume. A consequence of the decline in recorded sputum volume which took place in the earlier part of the study (Table 4.4 and Fig. 4.5, p. 61) was an association between changes in mean sputum volume and attendance pattern, for a man who attended the first three surveys but missed several later surveys would tend to have a larger mean sputum volume than a man with a similar degree of mucus hypersecretion who had attended every survey. Simple regressions of sputum volume would also be affected by attendance pattern. A probit transformation was therefore used (Appendixes, section B.8). Mean sputum probits and regressions of sputum probits on time were calculated for each man. (In addition to removing associations with attendance patterns, this transformation produces deviations about regression lines which have an approximately normal distribution.) Mean sputum volumes and their regression on time were also used.

Questions on phlegm production. At every summer survey, each man was asked the following standard questions about phlegm production. (The numbers are those given to the corresponding questions in the Medical Research Council (1966*a*) Questionnaire on Respiratory Symptoms.)

6. Did you usually bring up phlegm from your chest first thing in the morning last winter?
8. Did you usually bring up phlegm from your chest during the day last winter?

10. (If yes to 6 or 8) Did you bring up phlegm like this on most days for as much as three months last winter?

In previous reports of the results of the study, the answers to these questions were graded in two categories (ignoring questions 6 and 8), scoring 0 for No and 1 for Yes to question 10. To see whether this two-point scale could usefully be extended, the answers to phlegm questions asked at every summer survey were tabulated against the mean FEV and the mean sputum volume at those surveys (Table 2.5). The five-point scale suggested (Appendixes, section B.8; Fletcher *et al.* 1974) by the data in Table 2.5 is indicated in the final column of the table. We therefore scored the answers to questions 6, 8, and 10, as 2, 1, and 1 respectively, giving each man a 'phlegm score' at each summer survey 1962–9 of 0, 1, 2, 3, or 4. Finally, we calculated a 'mean phlegm score 1962–9' for each of the 792 men in the Follow-Up Group, which ranges from 0·0 (no chronic phlegm reported at any summer survey) upwards to a maximum of 4·0.

Drawbacks of our indices of mucus hypersecretion. Hypersecretion in the small airways may remain largely undetected, and even in the larger airways neither questions about expectoration nor measurements of sputum volume provide accurate measurements of the amount of bronchial mucus secretion. The men were asked to expectorate into the bottles all the phlegm 'coming from their chests' during the first hour in the morning, but this requirement cannot be relied on, because of forgetfulness and carelessness, and also because some men left for work within this hour and would be unlikely to use their bottles after they had left home. The technique ignores men who expectorate later in the day but not first thing in the morning, although this does not appear to be an important source of error, for Table 2.5 shows that morning phlegm is more closely related to FEV reduction than daytime phlegm is.

Errors due to day-to-day variations in expectoration were reduced, but not excluded, by using the mean volume of three specimens collected in successive weeks after each survey. Inevitably some men failed to return bottles. The proportion of men in the Follow-Up Group who failed to return any sputum bottles (Table 2.6) varied between 3 per cent at the first and 16 per cent at the eleventh survey, the average failure rate being 10 per cent. The failure rate was considerably higher in the Lapses. It tended to be slightly higher in men with smaller than in men with larger volumes of sputum (Table 2.5).

Table 2.5. Scoring the phlegm questionnaire replies

Relationship between answers to the phlegm questionnaire at summer surveys from 1962 to 1969 and the return of sputum specimens, sputum volume, and FEV at those surveys

Question 6 (morning phlegm)	Question 8 (daytime phlegm)	Question 10 (3-month phlegm)	No. of bottles		Non-empty bottles as percentage of returned	Mean sputum volume (ml)		Mean FEV (litres)	Score
			Returned	Not returned		In returned bottles	In non-empty bottles		
No	No	No	3206	427 (11·8%)	13·3	0·20	2·15	3·24	0
Yes	No	No	408	54 (11·7%)	55·4	1·23	2·31	2·93	2
No	Yes	No	338	43 (11·3%)	24·4	0·40	1·85	3·08	1
Yes	Yes	No	220	22 (9·1%)	56·8	1·54	2·79	2·77	3
Yes	No	Yes	690	64 (8·5%)	79·1	2·18	2·78	2·84	3
No	Yes	Yes	140	14 (9·1%)	46·4	0·74	1·70	2·94	2
Yes	Yes	Yes	801	81 (9·2%)	87·8	3·02	3·45	2·67	4
	All men		5803	705 (10·8%)	37·5	0·97	2·76	3·07	—

Table 2.6. Failure to return phlegm bottles 1961–9

Survey no.	Year	Winter or summer	Number of men attending survey: Follow-Up Group	Lapses	Men not returning sputum bottles: Follow-Up Group No.	Follow-Up Group Per cent	Lapses No.	Lapses Per cent	Total No.	Total Per cent
1	1961	S	792	344	24	3	21	6	45	4
2		W	758	263	34	4	16	6	50	5
3	1962	S	742	241	32	4	18	7	50	5
4		W	722	220	46	6	20	9	66	7
5	1963	S	727	225	77	11	38	17	115	12
6		W	725	190	69	10	31	16	100	11
7	1964	S	717	172	57	8	35	20	92	10
8		W	688	151	59	9	24	16	83	10
9	1965	S	690	131	47	7	19	15	66	8
10		W	684	93	96	14	17	18	113	15
11	1966	S	714	98	116	16	32	33	148	18
12		W	—	—	—	—	—	—	—	—
13	1967	S	644	29	77	12	5		82	12
14		W	701	23	77	11	1		78	11
15	1968	S	685	14	67	10	0	10	67	10
16		W	676	15	70	10	3		73	11
17	1969	S	682	6	86	13	0		86	13
3–17†	1962–9†	—	9797	1608	976	10	243	15	1219	11

† Sputum volumes at first two surveys excluded from analysis of data.

Evidence of mucus hypersecretion derived from standard questions on phlegm production is only crudely quantitative and suffers from errors due to misunderstanding of the questions and from failure of recollection. Since it was found in the analysis of the follow-up results (Fletcher *et al.* 1974; Appendixes, section B.8) that the answers to questions about phlegm were better predictors of mean FEV than were measurements of sputum volume, these answers provide at least as good an index of the presence or absence of mucus hypersecretion. They are certainly easier to obtain and are free from missing values due to failure to return sputum bottles.

Recording of smoking habits

Each man's current smoking habits were recorded at each summer survey. At the ninth survey a questionnaire (Appendixes, section A.5) about lifetime smoking habits was completed by the 821 men who attended. For different purposes in different analyses, the men were divided into various groups on the basis of their smoking habits during the course of the study (Appendixes, section B.8). The chief point to note is that whenever we talk of *non*-smokers, we mean *lifelong* non-smokers.

We also calculated the average reported cigarette consumption, and the rate of change of cigarette consumption as the regression on calendar year of the daily cigarette consumption rates reported at the summer surveys (Appendixes, section B.4). For men who always smoked some cigarettes, we calculated the mean, over all summer surveys attended, of the proportions (scoring the answers to part V on p. 158 0, $\frac{1}{4}$, $\frac{3}{4}$, or 1) of their cigarettes which were said to be filter-tipped and their rate of change of filter-tip usage (the regression on calendar year of these proportions).

Personal and family history of allergy

Questionnaires. In the original design of the study, no provision was made for investigation of allergy, apart from questions about a personal and family history of asthma and hay fever asked at the initial survey in 1961 (Appendixes, section A.3). In 1965, Professor J. Pepys asked if he might look for evidence of allergy in the men in our sample, most of whom were quite healthy. For this purpose, a standardized questionnaire on allergy was devised (Appendixes, section A.6) and applied to the 219 men at the Post Office Savings Bank at the tenth survey in January 1966. The allergy questionnaire was also applied to the 496 men at the London Transport Workshops who attended the summer survey of 1967. A 'family history' variable was extracted, being negative (0) for no

mention of eczema, urticaria, hay fever, or migraine in any first-degree relative, and positive (1) otherwise.

Questions on asthma were asked at the initial survey in 1961 (Appendixes, section A.3, question 52) and at a later survey as part of the allergy questionnaire (section A.6, question 6). There were considerable discrepancies between the replies given at these two surveys by the men who attended both. We therefore decided to look at all the available evidence on the men in the Follow-Up Group who said that they had asthma on either occasion. We concluded that 17 of them had clinical asthma during the course of the study. The (rather unsatisfactory) grounds for this diagnosis are given in section E.2 of the Appendixes.

Sputum eosinophilia

This was assessed by the technique of Mulder (1956) in which wet smears stained with eosin are placed into four grades according to the proportion of eosinophil cells (Miller and Jones 1963). Assessments of sputum eosinophilia were made on all sputum specimens returned at the second, seventh, and ninth surveys. The maximum grade of the nine (or fewer) specimens available was used in the regression analyses.

Other studies

Childhood illnesses. At the fifth survey, in 1963, a special questionnaire (Appendixes, section A.7) on childhood illnesses was applied to non-smokers who produced sputum and to age-matched groups of cigarette smokers who did and who did not produce sputum (Fletcher 1965). At the thirteenth survey in 1967, the same questionnaire was applied to all the men who attended. Only the answers to these questions in 1967 were used in the multiple regression analysis, scoring 0 for a negative and 1 for a positive history before the age of 15 separately for each disease.

Chest X-rays. At the thirteenth survey in 1967, full-sized postero-anterior and lateral chest X-rays were taken of 568 of the men who were still attending the main centres. A mobile unit provided by the Medical Research Council's Pneumoconiosis Research Unit was used. Some of the men who had moved employment since the beginning of the study came to Hammersmith Hospital for their X-rays. These X-rays were read by Dr. G. Simon and classified into three categories: 0—no definite emphysema; 1—definite localized emphysema; and 2—definite generalized emphysema. These scores were used in the regression analyses. The methods and reliability of these X-ray readings are described and discussed in Appendix D.

Skinfold thickness. At the thirteenth survey, in 1967, following a report of reduced skinfold thickness in men with airflow obstruction (Smith *et al.* 1967), the men who attended that survey had measurements made of skinfold thickness on the backs of their hands.

Measurements not analysed in this book. In the course of the study various subsidiary investigations were carried out, the results of which were not used in the follow-up analysis. In 1962, Dr. D. L. Miller carried out a study of the bacterial flora of the upper respiratory tract and sputum on a sample of the men at the London Transport Workshops (Miller and Jones 1964). In 1965, Dr. A. Levin investigated heart-rate changes after the Valsalva manoeuvre on men at the Post Office Savings Bank (Levin 1966), and in 1966 dietary histories were taken from men at London Transport Workshops as part of a study of the relationship of sugar intake to coronary heart disease (Medical Research Council 1970). Measurements of blood-pressure (Rose *et al.* 1964) were made at each of the summer surveys from 1961 to 1966, and electrocardiograms were recorded at the 1961, 1963, and 1965 surveys (Armitage *et al.* 1966; Prineas *et al.* 1968; Rose, 1971). Questions on angina were also asked at these surveys (Rose 1968).

Questions about whether the men slept with their bedroom windows open were asked because it had been suggested that the high prevalence of disabling bronchitis in the United Kingdom might be due to the tendency of many British people to sleep with their bedroom windows open in all weathers (Fletcher 1959). Twenty-two per cent of men said that they always had their bedroom windows open, and a further 44 per cent kept them open except in foggy weather. Since few men would have had central heating, two-thirds of them must have had cold bedrooms in winter, although for the most part they shut out winter fog. We have made no further use of the replies to these questions.

Data processing

A file was kept for each man into which the results were placed in sequential order. After each survey had been completed, the data for each man were coded in numerical form and entered onto a record card. These cards were used for preliminary analyses carried out in the course of the study. The data were also entered onto a transcription sheet and punched onto five-hole (later seven-hole) paper tape. The data on the paper tape were printed out and checked against the original survey records. They were then further checked by the computer for acceptability of range and some residual errors

were corrected. Finally the corrected data were transferred to Atlas magnetic tape. Additional paper tapes were made for some of the special studies. The statistical handling of the data is described in Appendix B.

3 The initial survey

Summary

THE HYPOTHESES studied in Chapters 5–7 were derived from cross-sectional surveys. Treating the initial (1961) survey in our study as a cross-sectional survey, we find that the mean FEV level and the prevalences of current smoking, persistent phlegm, recent chest illnesses, and dyspnoea are comparable with those reported in other cross-sectional surveys, and that the expected correlations of these factors with each other and with age and FEV are also present. This is true both in the total co-operative population from which our random sample was drawn, and in the Follow-Up Group who eventually attended for most of the eight years of the study. Our methods and study population are therefore fairly ordinary, and our inferences in Chapters 5–7 about the absence of certain causal connections are thus a valid extension of the cross-sectional studies which originally gave rise to the various postulates about causality which this study was designed to test. The sole purpose of the 1961 data presented in this chapter is to characterize the population being studied: in view of the extent of the data presented in later chapters, no epidemiological interpretation of the 1961 data has been attempted.

Comparability with other surveys

Previous 'cross-sectional' surveys (i.e. surveys done at one particular time) had generated various hypotheses about the causal relationships that might exist between mucus hypersecretion, chest infections, smoking, and flow obstruction (Chapter 1). The data we collected between 1961 and 1969 fail to confirm some of these hypotheses, and it may therefore be wondered whether some peculiarity, either of our methodology or of our study population, somehow invalidates our conclusions.

If viewed in isolation from the subsequent findings, the initial (1961) survey is itself a substantial cross-sectional survey, free of the training effects that may have affected data collected at subsequent surveys. The findings at the initial survey should, therefore, be broadly comparable with the findings at other such surveys. To show that this is so, we have tabulated the prevalences of various factors that we would have found had our 1961 sample been a purely random

Table 3.1. 1961 characteristics of Follow-Up Group and total co-operative population

	Follow-Up Group	Estimate for total co-operative population
Number of men	792	2601
Mean age in 1961 + 0·5	47·1	47·6
Percentages of:		
non-smokers	13·3	9·8
ex-smokers	16·8	16·7
cigarette smokers	64·4	67·7
Percentage with persistent phlegm all day	25·0	16·4
Mean sputum volume (ml) if bottle seen	1·6	1·4
Percentage with one or more chest illnesses in past 3 years	25·1	16·0
Percentage with breathlessness grade 2+†	29·2	25·7
Mean FEV (litres)	3·22	3·21
Percentage with FEV <2·0 litres	4·3	4·8

† See Table 3.10 on p. 43 for definition of grade 2.

(unstratified) sample of all the eligible men at the London Transport Workshops or Post Office Savings Bank who were prepared to co-operate with us.

From the actual proportions of those selected who did co-operate by coming to the 1961 survey, we estimate that this total co-operative population would have consisted of about 2601 of the 3013 eligible men (Fig. 2.2, p. 19). The prevalences that would have been found in the total co-operative population can be estimated in the usual way from the prevalences observed in the stratified sample of 1136 men who actually did attend the 1961 survey.

From the total co-operative population we derived the stratified sample of 1136 men in 1961; 344 of the stratified sample lapsed during the next few years, and the detailed inferences made in Chapters 5, 6, and 7 are based on the results in the remaining 'Follow-Up Group' of 792 men. It happens that the effects of weighting the 1961 sample with symptomatic men were approximately cancelled by the greater subsequent lapse rate among these symptomatic men, and so (Table 3.1) the findings in the Follow-Up Group were similar to, although not identical with, those which would have been observed in the total co-operative population.

We have therefore compared various factors recorded in 1961 in the Follow-Up Group with observations of those factors in other employed groups (Table

Table 3.2. 1961 characteristics of the Follow-Up Group compared with other groups of employed men

Reference	Place of work and occupation of men studied	Number of men	Ages	Mean height (cm)	Mean FEV (litres)	Current smokers (per cent)	Persistent cough (per cent)	Persistent phlegm (per cent)	Recent chest illness (per cent)	Dyspnoea grades 3 or 4 (per cent)
Fletcher *et al.* (this study)	London, England: engineering and clerical (Follow-Up Group)	792	30–59	171·8	3·22	70	38	38	25	6
Fletcher *et al.* (1959)	London, England: postmen	192	40–59	—	3·13	86	30	39	39	9
Holland and Reid (1965)	London, England: van drivers/engineers	280	40–59	—	3·11	80	19	15	19	5
Holland and Reid (1965)	Country towns, England: van drivers/engineers	426	40–59	—	2·76	75	36	30	23	3
Sharp *et al.* (1965)	Chicago, USA: light industry	1887	43–58	—	3·01	69	19	20	10	4
Holland *et al.* (1965)	USA East Coast: telephone men	625	40–59	—	3·50	72	31	32	22	—
Densen *et al.* (1967, 1969)	New York, USA: postal and transit workers	9442	All ages	—	3·15	81	19	23	17	2
Mork (1962)	Bergen, Norway: transport workers	189	40–59	—	3·03†	84	33	24	15	4
Khosla and Lowe (1972)	Ebbw Vale and Port Talbot, South Wales: steel workers	5117	30–59	170·7	3·11	72	40	29	18	16
		8651	30–59	172·0	3·39	63	34	26	17	10

† FEV estimated from mean peak expiratory flow by regression equation of Fairbairn *et al.* (1962).

Table 3.3. 1961 characteristics of the Follow-Up Group compared with those reported in general population samples

Reference	Place	Number of men	Ages	Mean height (cm)	Mean FEV (litres)	Current smokers (per cent)	Persistent cough (per cent)	Persistent phlegm (per cent)	Recent chest illness (per cent)	Dyspnoea grade 3 or 4 (per cent)	Notes
Fletcher *et al.* (this study)	London, England	792	30–59	171·8	3·22	70	38	38	25	6	
Higgins and Cochrane (1961)	Rhondda Fach, Wales (non-miners)	176	35–54	169·9	3·10	73	36	32	13	5	
Ferris and Anderson (1962)	Berlin, New Hampshire, USA	349	35–64	170·4	2·71	64	37	33	7	3	Half the men were over 55 years old
Payne and Kjelsberg (1964)	Tecumseh, USA	1454	30–59	173·8	3·13	63	48	—	11	—	Cigarette smokers; ignoring other tobacco
Anderson *et al.* (1965)	Chilliwack, Canada	161	35–64	—	3·22	49	21	26	4	5	
Huhti (1965)	Harjavatta, Finland	653	40–64	170·9	3·31	60	25	30	14	12	
Cullen *et al.* (1969)	Busselton, Western Australia	942	30–59	184·9	3·76	54	9	8	5	1	Height given in personal communication
Van der Lende (1969)	Meppel, Holland	1709	40–60	176·2	3·08	80	21	15	—	5	
Van der Lende (1969)	Vlagtwedde, Holland	902	40–60	172·3	3·05	84	23	14	9	7	
Van der Lende (1969)	Vlaardingen, Holland	508	40–60	173·9	3·24	74	31	27	13	6	Only 14 per cent of men were over 55
Sawicki (1972)	Cracow, Poland	909	30–59	170·0	3·79	65	24	29	18	7	

3·3). It may be seen that our findings are, in these contexts, ordinary. This suggests that our results are as generally applicable as the hypotheses, derived from such cross-sectional studies, which our study was designed to test.

The rest of this chapter is concerned with the detailed characteristics of our population. It need be studied only by readers who are concerned with any special bias or other relevant problem.

Detailed results of the initial (1961) survey

There were more older men at the London Transport Workshops than at the Post Office Savings Bank (mean ages 46 and 39 in 1961 respectively). The proportions of smokers were similar at both places but there were slightly more heavy smokers at the Post Office Savings Bank. After adjustment for these differences, the mean FEV levels and the prevalence of respiratory symptoms in the two groups of men were similar, and the findings in both groups have therefore been combined.

Table 3.4. Percentage age distribution at initial survey, 1961

Age group in 1961	Estimate for total co-operative population	Stratified sample (1136 men)	Follow-Up Group (792 men)	Lapses, as a percentage of stratified sample
30–34	5·2	6·1	5·6	36
35–39	13·2	12·9	14·8	20
40–44	20·4	18·5	19·7	26
45–49	19·5	19·7	20·6	27
50–54	19·0	19·5	19·6	30
55–59	22·7	23·3	19·8	41
All men	100·0	100·0	100·0	30

Age, height H, and smoking habits

Age (Table 3.4). The age structure of the stratified sample was not very different from that of the population from which it was drawn, but during the course of the study, death, disablement, and premature retirement resulted in a slight reduction in the proportion of men initially aged 55–59 in the Follow-Up Group.

Height (Table 3.5). The older men were shorter than the younger men. The mean heights in the total co-operative population are compared in Table 3.5 with those of other British industrial populations (Khosla and Lowe 1968). These populations all show a similar diminution of stature with age. Khosla and Lowe considered this to be a cohort effect due to the secular increase in adult male height which

Table 3.5. Height in this and in other series

Mean standing height (cm, without shoes) in total co-operative population, initial survey, 1961, and in four other British working populations (Khosla and Lowe 1968)

Reference	Population studied	Age					
		30–34	35–39	40–44	45–49	50–54	55–59
Fletcher *et al.* (this study)	Estimate for total co-operative population	175·5	172·3	173·2	171·9	170·2	169·0
Lowe *et al.* (1968)	10 863 men employed by steel company	174·0	173·0	172·0	171·2	170·4	169·9
Lowe and McKeown (1962)	5259 men employed in electrical engineering	173·5	172·7	172·0	171·2	170·2	169·4
Kemsley (1950)	27 515 men employed in various industries	169·4	169·2	167·9	167·4	166·9	166·6
Cathcart *et al.* (1935)	10 590 men employed in various industries	169·7	169·4	168·7	168·4	167·9	166·9

Table 3.6. Percentage distribution of smoking habits by age at initial survey, 1961

Smoking habits	UK 1961 men aged 35–59	Estimate for total co-operative population	Stratified sample (1136 men)	Follow-Up Group				Lapses as percentage of stratified sample
				Age 30–39 (161 men)	Age 40–49 (319 men)	Age 50–59 (312 men)	All ages (792 men)	
Non-smokers	9	9·8	12·4	21·1	14·7	7·7	13·3	26
Ex-smokers	16	16·7	15·2	15·5	13·5	20·8	16·8	23
Pipe/cigar smokers	5	5·8	5·2	5·6	6·3	4·8	5·6	25
Cigarette smokers (with mean daily consumption)	69 (13·2)	67·7 (14·3)	67·2 (15·0)	57·8 (15·3)	65·5 (14·6)	66·7 (16·0)	64·4 (15·3)	33

has been observed in Western Europe since 1850 and is still in progress.

Smoking habits (Table 3.6). The proportions of non-smokers, ex-smokers and smokers in the total co-operative population were similar to those reported for all men aged 35–39 in the United Kingdom in 1961 (Todd 1972). The proportion of non-smokers was greater in the stratified sample and Follow-Up Group owing to the higher sampling fraction used for these men, most of whom were asymptomatic. One-third of the cigarette smokers lapsed compared with a quarter of the other men.

Prevalence of respiratory symptoms

Cough and phlegm (Table 3.7). About a quarter of the men in the total co-operative population admitted to persistent cough and to persistent phlegm. This proportion was greater in the stratified sample owing to the higher sampling fraction used for these men. The lapse rate was not closely related to these symptoms, so that the proportion of men with cough and with phlegm remained higher in the Follow-Up Group than in the total co-operative population.

Sputum volume (Table 3.8). For similar reasons, the proportion of men who produced a sputum specimen was greater in the stratified sample than in the total co-operative population. Men aged 50–59 had higher mean sputum volumes than did younger men. The high proportion of lapses among those who did not return a bottle presumably represents an association between poor motivation in both returning bottles and continuing to attend.

Chest illnesses (Table 3.9). The frequency of reporting a recent history of chest illness was considerably lower in the total co-operative population than in the Follow-Up Group.

Breathlessness on exertion (Table 3.10). Breathlessness was graded as recommended in the Medical Research Council's (1966*a*) standardized questionnaire on respiratory symptoms. There was a higher proportion of men with breathlessness of all grades in the stratified sample than in the total co-operative population. The proportion of men in the stratified sample who lapsed increased strikingly with increasing grade of breathlessness, so that the Follow-Up Group had a distribution similar to the total co-operative population.

Forced expiratory volume (Table 3.11; Fig. 3.1). FEV declined approximately linearly with age, and in each age group was similar in the total co-operative population and in the Follow-Up Group.

Table 3.7. Percentage distribution of chronic phlegm and of chronic cough by age at initial survey, 1961

Grade of cough or grade of phlegm	Estimate for total co-operative population	Stratified sample (1136 men)	Follow-Up Group				Lapses as percentage of stratified sample
			Age 30–39 (161 men)	Age 40–49 (319 men)	Age 50–59 (312 men)	All ages (792 men)	
No cough (No to questions 1 and 3)	59·2	48·2	58·4	48·6	44·2	48·9	29
Infrequent cough (Yes to questions 1 or 3, no to question 5)	13·5	12·9	14·9	10·0	16·0	13·4	27
Persistent cough part day (Yes to question 5, no to questions 1 or 3)	11·0	12·6	9·3	16·0	13·8	13·8	24
Persistent cough all day	16·3	26·3	17·4	25·4	26·0	24·0	36
No phlegm (No to questions 6 and 8)	59·7	46·0	54·7	47·6	45·2	48·1	27
Infrequent phlegm (No to question 10, yes to questions 6 or 8)	13·8	14·2	16·8	12·2	14·1	13·9	32
Persistent phlegm part day (Yes to question 10, no to questions 6 or 8)	10·2	12·9	9·3	12·5	15·4	13·0	29
Persistent phlegm all day	16·4	27·0	19·3	27·6	25·3	25·0	36

Table 3.8. Percentage distribution of sputum volume by age at initial survey, 1961

Sputum volume (ml)	Estimate for total co-operative population				Stratified sample (1136 men)	Follow-Up Group				Lapses as percentage of stratified sample
	Age 30–39	Age 40–49	Age 50–59	Total		Age 30–39 (161 men)	Age 40–49 (319 men)	Age 50–59 (312 men)	Total (792 men)	
0	63·3	62·8	59·2	61·4	51·8	59·6	58·0	49·4	54·9	26
0·1–1·9	18·0	13·8	11·1	13·5	15·2	17·4	15·7	15·1	15·8	28
2·0–4·9	3·4	10·0	6·2	7·2	8·9	6·2	11·0	7·7	8·7	32
5·0+	8·9	10·0	18·9	13·5	20·2	14·3	12·9	24·0	17·6	39
Bottle not returned	6·4	3·4	4·6	4·5	4·0	2·5	2·5	3·8	3·0	47
Mean sputum volume in returned bottles	1·0	1·1	1·7	1·4	1·9	1·5	1·3	2·1	1·6	—

Table 3.9. Percentage distribution of chest illnesses at initial survey, 1961

		Estimate for total co-operative population	Stratified sample (1136 men)	Follow-Up Group (792 men)	Lapses as percentage of stratified sample
No chest illnesses involving a week off work in past 3 years		84·0	72·5	74·9	28
One or more such chest illnesses in past 3 years	All without increased phlegm	6·7	9·9	9·0	37
	One or more with increased phlegm	9·3	17·6	16·2	36
One or more periods of increased cough and phlegm lasting 3 weeks or more during past 3 years		17·0	25·2	23·2	36

Table 3.10. Percentage distribution of breathlessness by age at initial survey, 1961

Breathlessness grade	Estimate for total co-operative population				Stratified sample (1136 men)	Follow-Up Group				Lapses as percentage of stratified sample
	Age 30–39	Age 40–49	Age 50–59	Total		Age 30–39 (161 men)	Age 40–49 (319 men)	Age 50–59 (312 men)	Total (792 men)	
1. No breathlessness	90·1	79·5	62·5	74·3	66·0	85·1	72·1	62·2	70·8	25
2. Breathless hurrying on level or walking up a slight hill	8·7	17·1	27·1	19·7	25·2	13·7	21·9	28·8	23·0	36
3. Breathless walking on level	1·0	3·3	8·4	5·0	7·3	1·2	5·6	7·7	5·6	47
4. Unable to continue on level	0·2	0·1	0·8	0·4	1·0	0	0·3	0·6	0·4	73
Disabled by other disease	0·0	0·0	1·3	0·5	0·5	0	0	0·6	0·3	67

Table 3.11. FEV† by age at initial survey, 1961

Age	Estimate for total co-operative population	Stratified sample (mean ±S.D.)	*Follow-Up Group* (mean ±S.D.)	*Lapses* (mean ±S.D.)
30–34	3·91	3·80 ±0·71	3·93 ±0·68	3·58 ±0·72
35–39	3·68	3·64 ±0·62	3·63 ±0·60	3·67 ±0·70
40–44	3·58	3·45 ±0·71	3·50 ±0·68	3·32 ±0·80
45–49	3·21	3·14 ±0·60	3·20 ±0·58	2·98 ±0·60
50–54	2·99	2·93 ±0·67	2·99 ±0·59	2·77 ±0·82
55–59	2·61	2·55 ±0·69	2·67 ±0·62	2·37 ±0·75
All ages	3·21	3·12 ±0·78	3·22 ±0·72	2·91 ±0·87

† Maximum of last three of five readings (BTPS).

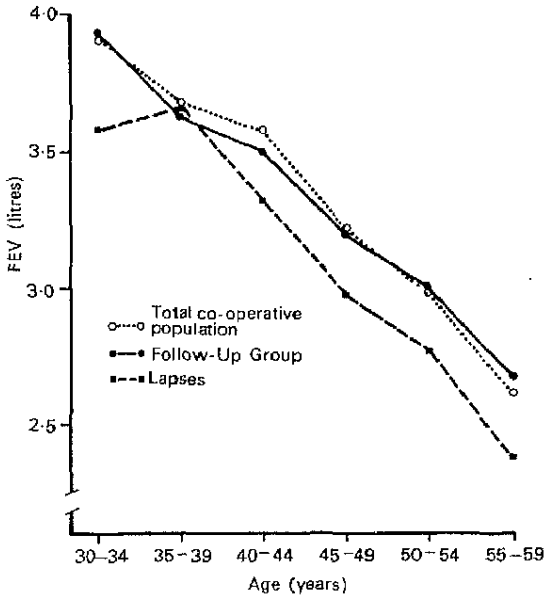


Fig. 3.1. FEV by age

Mean FEV at the initial survey, 1961 by age in total co-operative population, Follow-Up Group and Lapses.

Values for the Lapses tended to be lower. The explanation of the almost identical standard deviations of the means in each age group is considered in section B.9 of the Appendixes.

Regression of FEV on age and height (Table 3.12; Fig. 3.2). Regression coefficients of FEV on age were similar in the total co-operative population, the Follow-Up Group, and the Lapses. The

Table 3.12. Regression of FEV on height and age, initial survey, 1961

h = (height in metres − 1·7)
a = (age in years − 50)

Stratified sample (1136 men)	$FEV = 2{\cdot}93 \pm 0{\cdot}61 + 3{\cdot}8h - 0{\cdot}046a$
Follow-Up Group (792 men)	$FEV = 3{\cdot}01 \pm 0{\cdot}56 + 3{\cdot}6h - 0{\cdot}046a$
Lapses (344 men)	$FEV = 2{\cdot}79 \pm 0{\cdot}63 + 4{\cdot}7h - 0{\cdot}042a$
Non-smokers (141 men)	$FEV = 3{\cdot}28 \pm 0{\cdot}53 + 3{\cdot}8h - 0{\cdot}026a$
Cigarette smokers (763 men)	$FEV = 2{\cdot}87 \pm 0{\cdot}61 + 3{\cdot}5h - 0{\cdot}048a$
Asymptomatic† (110 men: sample group 3)	$FEV = 3{\cdot}01 \pm 0{\cdot}59 + 3{\cdot}8h - 0{\cdot}037a$
Symptomatic† (479 men: sample group 1)	$FEV = 2{\cdot}76 \pm 0{\cdot}63 + 3{\cdot}4h - 0{\cdot}050a$
Cotes *et al.* (1966)	$FEV = 3{\cdot}19 \pm 0{\cdot}50 + 3{\cdot}6h - 0{\cdot}031a$

† These regressions may be misleading: see text.

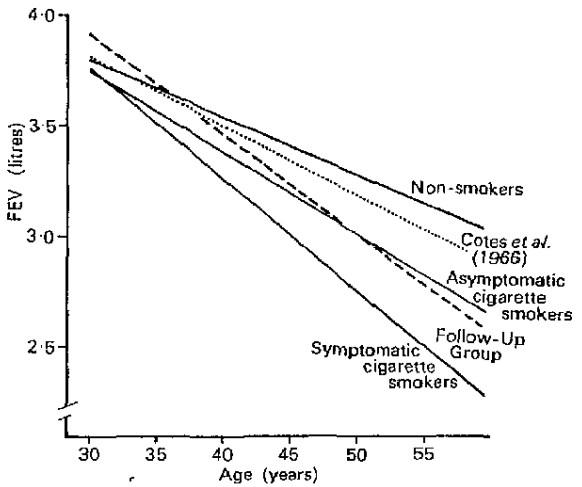


Fig. 3.2. FEV by age given height.

Relationship with age in the regression of FEV on age and height at the initial survey, 1961, in various subgroups of men (from Table 3.12). The symptomatic and asymptomatic lines may be misleading: see text.

regression coefficients on age were steeper in the smokers than in the non-smokers, and steeper in the symptomatic than in the asymptomatic men. (This latter comparison is included for comparability with other studies, but must be interpreted with caution since men

Table 3.13. Percentage distribution of standardized SFEV†, initial survey, 1961

SFEV (litres)	Estimate for total co-operative population	Stratified sample (1136 men)	Follow-Up Group (792 men)	Lapses as percentage of stratified sample
<2	4·8	7·1	4·8	53
2·0–	9·7	11·8	10·7	37
2·5–	27·1	27·8	26·0	35
3·0–	35·6	33·3	37·0	22
3·5–	19·5	17·3	18·8	24
4·0+	3·3	2·6	2·7	30
All men	100·0	100·0	100·0	30
Mean SFEV	3·07	2·98	3·05	—

† Maximum of last three of five readings $+0{\cdot}031a - 3{\cdot}62h$ (see Table 3.12).

may become symptomatic as they age, and change from one line to the other.) The regression coefficients on height were similar in all groups except for a slightly higher value in the Lapses. These regression coefficients are close to these reported for men by various other observers and summarized by Cotes *et al.* (1966).

Standardization of FEV for age and height. To standardize FEV values of smokers and non-smokers by their own regression coefficients would obscure real differences between these groups. The equation of Cotes *et al.* (1966), derived from a number of independent studies of healthy Caucasian men (Table 3.12), was used to standardize each man's FEV to age 50 and height 170 cm. The regression coefficient on height in this equation is identical to that in the Follow-Up Group. The age regression, intermediate between the healthy smokers and the non-smokers in the stratified sample, is rather smaller than in the Follow-Up Group which included men with symptoms. The FEV values used for standardization were the maximum of the last three of the five readings recorded in 1961 (Appendixes, section B.1), uncorrected in any way; these standardized FEV values are referred to as SFEV.

Frequency distribution of SFEV (Table 3.13). The difference between our study of employed men and a clinical series of patients is emphasized by the scarcity of SFEV values below two litres.

Interrelationships of the main components of the bronchitis syndrome with smoking habits and with each other

Smoking habits and sputum production (Table 3.14). As would be expected, sputum production depended very strongly on smoking habits. (Men not returning bottles are omitted.)

Table 3.14. Expectoration by smoking habits, initial survey, 1961

Smoking habits	Estimate for total co-operative population: Percentage of men with sputum ±S.E.	Estimate for total co-operative population: Mean sputum volume (ml) ±S.E.
Non-smokers	14±4	0·3±0·2
Ex-smokers	26±4	0·8±0·3
Pipe/cigar smokers	26±8	1·1±0·5
All cigarette smokers	42±2	1·7±0·2

	Follow-Up Group: Percentage of men with sputum ±S.E.	Follow-Up Group: Mean sputum volume (ml) ±S.E.	Follow-Up Group: Number of men who returned a sputum bottle
Non-smokers	16±4	0·5±0·2	104
Ex-smokers	34±4	1·1±0·3	128
Pipe/cigar smokers	39±7	1·3±0·4	44
All cigarette smokers	52±2	2·0±0·2	492

Smoking habits and SFEV (Table 3.15; Fig. 3.3). Mean SFEV was highest in the non-smokers, intermediate in ex-smokers and pipe and cigar smokers, and lowest in the cigarette smokers. Among the latter, the lowest mean value, especially in the total co-operative population, was in the small group who smoked less than 5 cigarettes/day, but there was a steady downward trend of mean SFEV with increasing consumption among the rest of the smokers. The relationship between FEV and smoking is discussed in more detail in Chapter 5.

Sputum production, smoking habits, and chest illnesses (Table 3.16). The interest of this table is that it is so misleading. Although, in common with the results of other prevalence surveys, it appears to demonstrate that, among those without mucus hypersecretion, there is still a relationship between smoking and chest illnesses, it is concluded in Chapter 6 that this apparent relationship is probably a statistical artefact arising because sputum volume is such an inaccurate index of mucus hypersecretion. This artefact is explained in more detail below.

Sputum production, chest illnesses, and low SFEV (Table 3.17; Fig. 3.4). The interrelationships between these three components of chronic non-specific lung disease are similar to those described in previous cross-sectional surveys (Fletcher *et al.* 1959; Fletcher and Tinker 1961), showing a steady decline of SFEV with increasing

Table 3.15. Smoking and SFEV (see Table 3.13) at initial survey, 1961

Smoking habits, 1961	Estimate ±S.E. for total co-operative population	Mean ±S.E. for Follow-Up Group
Non-smokers	3·28 ±0·05	3·33 ±0·06
Ex-smokers	3·16 ±0·06	3·12 ±0·05
Pipe/cigar smokers	3·18 ±0·09	3·15 ±0·09
All cigarette smokers	3·00 ±0·03	2·97 ±0·03
1–4 cigarettes/day	2·81 ±0·10	2·98 ±0·11
5–14 cigarettes/day	3·05 ±0·04	2·99 ±0·04
15–24 cigarettes/day	2·99 ±0·05	2·96 ±0·04
25+ cigarettes/day	2·94 ±0·07	2·91 ±0·07
All men	3·07 ±0·02	3·05 ±0·02

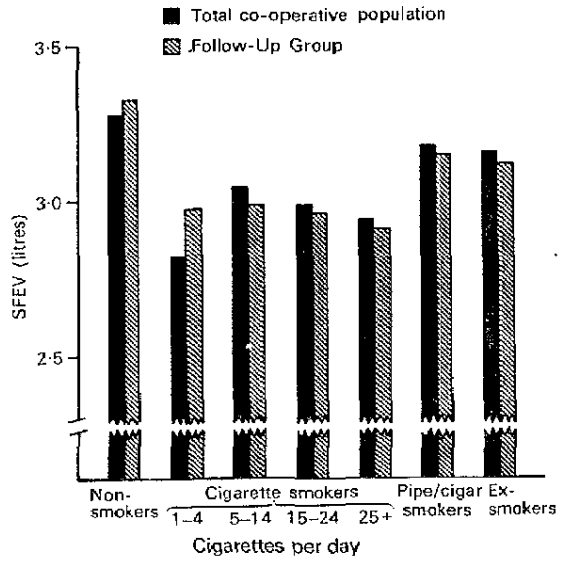


Fig. 3.3. SFEV by smoking

SFEV at the initial survey, 1961 by smoking habits in the total co-operative population and Follow-Up Group.

sputum volume and a lower SFEV in those with than in those without recent chest illnesses in each sputum volume group. We later conclude (Table 6.1, p. 107) that the latter finding is misleading, for the correlation between SFEV and chest illnesses arises chiefly because both are associated with mucus hypersecretion. But a single measurement of sputum volume is such an inaccurate measure of chronic

Table 3.16. Chest illnesses by smoking and expectoration

Frequency of reporting chest illnesses (with increase of phlegm) in relation to 1961 smoking habits and sputum volume

Sputum volume (ml)	Estimate for total co-operative population: Non- and [illegible] (percentage ±S.E.)	Estimate for total co-operative population: All men including nine [illegible] (percentage ±S.E.)	Follow-Up Group: Non- and [illegible] (percentage ±S.E.)	Follow-Up Group: All men including nine [illegible] (percentage ±S.E.)
0	3 ±2	6 ±2	6 ±2	11 ±2
0·1–1·9	11 ±8	11 ±4	23 ±8	19 ±4
2–4·9	8 ±10	12 ±5	14 ±9	20 ±5
5 or more	30 ±13	19 ±4	33 ±12	26 ±4
All men, including those who returned no sputum bottle	6 ±2	11 ±2	9 ±1	11 ±2	19 ±2	16 ±1

Table 3.17. SFEV (see Table 3.13) by 1961 sputum volume† and history of chest illness

Sputum volume (ml)	Chest illnesses with increased phlegm in past 3 years	Mean standardized FEV	
		Estimate for total co-operative population	Follow-Up Group (No. of men)
0	None	3·17	3·17 (386)
	One or more	2·91	2·99 (49)
0·1–1·9	None	2·99	3·04 (101)
	One or more	2·87	2·91 (24)
2·0–4·9	None	3·08	3·06 (55)
	One or more	2·49	2·77 (14)
5·0+	None	2·79	2·84 (103)
	One or more	2·66	2·67 (36)
All men	None	3·09	3·09 (645)
	One or more	2·79	2·86 (123)

† Excluding men who did not return their sputum bottle.

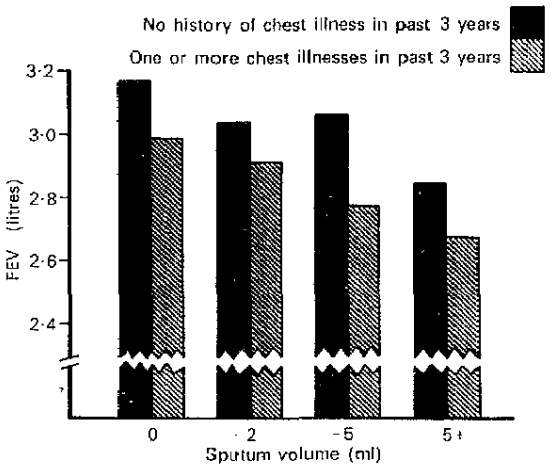


Fig. 3.4. SFEV by sputum and illness

SFEV at the initial survey, 1961 by sputum volume and chest illnesses in the Follow-Up Group.

mucus hypersecretion that, within a group of men whose 1961 sputum volumes (which were only recorded to the nearest millilitre) were all the same, there would be quite a variety of levels of chronic mucus hypersecretion. Within such a group of men, SFEV and chest illnesses will both be correlated with chronic mucus hypersecretion,

and hence with each other. Because of this, the correlation between SFEV and chest illnesses, shown in Table 3.17, is only slightly weaker within each sputum volume group than in all men. This gives a false impression that this correlation is independent of a common association with mucus hypersecretion.

Our analysis of the 1961 initial survey has convinced us that the Follow-Up Group of men were suitable for a study of the pathogenetic interrelationships of smoking, chest infections, airflow obstruction, and mucus hypersecretion, and that the observations made on them are likely to be of general relevance (see also Chapter 7).

4 Secular patterns of results during 1961 to 1969

Summary

We describe the survey-by-survey mean values recorded among members of the Follow-Up Group for smoking and for the three main components of chronic non-specific lung disease. It is usually difficult to distinguish between real trends and trends due to initial lack of experience with the test on the part of either the subjects or the observers.

FEV declined irregularly, being generally slightly lower in the winter than in the summer. The initial lack of training and the effects of the cold winter in 1962–3 appear to have depressed the earlier FEV values, making the overall rate of change of FEV appear to be only −30 ml/year instead of about −45 ml/year. The distribution of FEV slopes about their mean had a small 'tail' of very steep slopes. Smoking habits decreased by about 10 per cent after the first survey, and thereafter remained fairly constant. Recorded mucus hypersecretion decreased slightly during the first few years but was fairly constant thereafter, except for winter–summer fluctuations; we tentatively conclude that this initial decrease was real. Chest episodes were much more commonly reported in winter than in summer, but were otherwise reassuringly constant in frequency throughout the study, in parallel with a constant frequency of spells of sickness absence in the general population. Purulence frequency behaved erratically, possibly owing to observer variation.

General considerations underlying the study of changes during 1961 to 1969

When a measurement is made repeatedly, either by questionnaire or otherwise, the standards of response may vary owing to learning effects on the part of the subject or due to changes in the methods used by the observer. In addition to these inevitable biases, there are two further difficulties which are peculiar to our study.

First, although every man, whether in the Follow-Up Group or among the Lapses, attended the initial survey (for it attendance at the initial survey that the study popul defined), between 100 and 500 men (Fig. 2.1, p. 17) we from each subsequent survey. The probability of absence particular survey might be different among symptomatic men from the probability of absence among asymptomatic men and, if this is so, the changes in mean symptom frequency between different surveys will be biased by these selective absences. This bias can be largely overcome by ignoring the Lapses and studying the mean values of various quantities at each survey among those of the Follow-Up Group who attended that survey. This study of only the Follow-Up Group largely avoids biasing the pattern of changes by selective lapsing, and although slight biases due to selective sporadic absences could remain, they are unlikely to be appreciable since so few of the Follow-Up Group were absent at any particular survey (see Fig. 2.1, p. 17).

Secondly, our 1961 sample was not random: it was biased in favour of men who then had 'symptoms' (mainly mucus hypersecretion) and who were lifelong non-smokers. As years pass by, mucus hypersecretion may come and go. In those with hypersecretion in 1961, it can only stay or go. Changes in mucus hypersecretion (or anything correlated with it) in a population such as ours with an artificial excess of those who initially had hypersecretion will show an artificial excess of remissions by this process of 'regression towards the mean'. To avoid this, we have had to correct for the 1961 stratification by using our observations in the Follow-Up Group during 1961–9 to estimate (Appendixes, section B.7) the mean values of each factor which would have been observed in a Follow-Up Group derived from a purely random initial sample. This is what is done in each subsequent Figure or Table in this chapter which describes changes in mean values survey by survey. The importance of doing this is illustrated in Fig. 4.1, which gives the percentages of non-empty sputum bottles survey by survey in the Follow-Up Group among those who did and who did not admit to sputum production in 1961, and among all men. Although there is some decline during the first two years among 'all men', the significance of which will be discussed below, there is a much more marked decline during the first two years in the initially symptomatic men, which may be attributable in part to regression to the mean.

Forced expiratory volume in one second (FEV)

We expected that mean FEV values would decline at a steady rate. This expectation was not fulfilled. The observed pattern of change of

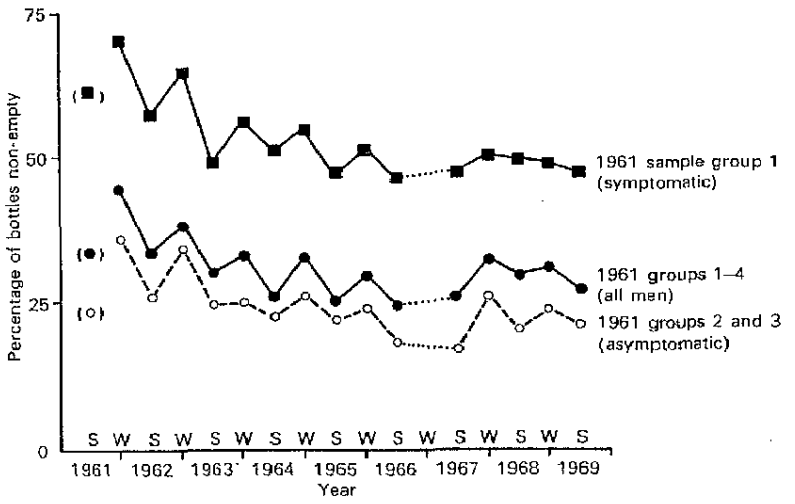


Fig. 4.1. Non-empty sputum bottles 1961–9

Percentages, corrected for 1961 stratification, of non-empty sets of sputum bottles at each survey among men in the Follow-Up Group who attended that survey and returned at least one bottle. (The S.E. of each point is about 2·5. The initial survey, based on one bottle instead of three, gives values which are biased downwards.)

FEV is best considered as it appeared in the 347 men who provided acceptable FEV readings at every survey, for this removes any distortion due to absence from one or more surveys of men with lower values of FEV (Table 4.1; Fig. 2.3, p. 22).

At the first four surveys there was a regular seasonal change in FEV, with higher values in the two summer surveys than in the winter surveys. The second winter, 1962–3, was exceptionally cold, the minimum temperature remaining below 0 °C every day between December and March. During this period, there was a sharp drop in mean FEV. There was a further decline in the July 1963 survey. As shown in Fig. 2.3 (p. 22), the rate of change of FEV during these first five surveys was −82 ml/year. The decline then levelled off, with little seasonal variation, until 1966, the rate of change during surveys 6–11 being only −14 ml/year. After this, the decline was resumed with regular seasonal variation and a rate of change of FEV of −26 ml/year. Over the whole study, the mean rate of change of FEV in the 347 men described in Fig. 2.3 (p. 22) was −30 ml/year, which happened also to be the mean among the whole Follow-Up Group. The short-term irregularities in the overall mean rates of loss of FEV are so large that we cannot usefully speculate about whether the

Table 4.1. FEV means and biases 1961–9

Mean FEV survey by survey of 347 men who gave acceptable readings at every survey, with individual observer biases at each survey†. These data are illustrated in Fig. 2.3 (p. 22).

Survey	Year	Mean FEV (litres)	Individual observer biases† (ml)
1	1961	3·339	+18, +14, −44
2	1961–2	3·276	+27, −2
3	1962	3·320	+11, 0, −14
4	1962–3	3·198	+20, +16, −7, −19
5	1963	3·172	+7, −49
6	1963–4	3·232	+36, +1, −11, −40
7	1964	3·187	+74, +11, −38
8	1964–5	3·193	+28, +13, +5, −61
9	1965	3·239	+30, −15, −31
10	1965–6	3·170	+3, +2, −6
11	1966	3·185	+28, −21, −28
12	—	No survey	—
13	1967	3·154	+36, −11
14	1967–8	3·034	+77, +49, +10, −58
15	1968	3·105	+24, −37, −48
16	1968–9	3·042	+53, +35, −14, −47
17	1969	3·084	+35, −30, −34

†See Appendixes, section B.2.

underlying mean rate of loss of FEV during the 1960s was steady or not. In section B.9 of the Appendixes it is shown that rates of loss of FEV tend to accelerate, but this effect would also be completely lost in the short-term irregularities.

The biases of the various observers at each survey (estimated as in section B.2 of the Appendixes) are shown in Fig. 2.3 (p. 22), and it will be seen that they are of a size which might account for some of the irregularity. There is no way of deciding whether the observed deviations from a steady decline of FEV are genuine or whether they were chiefly due to observer biases, although the fact that the most extreme deviations coincided with the coldest weather does suggest that some of the changes were real and that adverse climatic conditions may be able to depress the mean FEV of a whole group of men temporarily by at least 0·1 litres, in spite of great care being taken to keep the spirometer temperature constant.

Distribution of FEV slopes

The way in which the rate of loss of FEV for each man was estimated is described in detail in the Appendixes, sections B.1–B.5. Briefly, after minor bias corrections to the various FEV readings, for each man in the Follow-Up Group a regression line on calendar year was drawn through his FEV readings (ignoring those that differed by more than

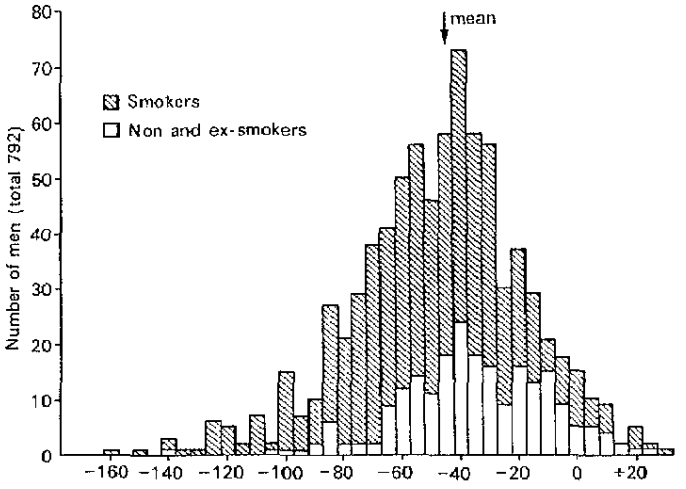


Fig. 4.2. FEV slope distribution

Distribution of FEV slope in the Follow-Up Group, rounded downwards by up to 5 ml/year, distinguishing between current smokers and other men. (FEV slope ≅ long-term rate of change ±25 ml/year due to short-term deviations and measurement errors.)

±450 ml from a line of slope 30 ml/year through his mean FEV level) and his rate of change of FEV during the study was estimated (see p. 125) as the slope of this regression line minus 15 ml/year. We consider (Appendixes, section B.3) that these estimated rates of change of FEV, which we call 'FEV slopes', differ randomly from the true rates of change with a S.D. which is of order ±20 ml/year. The distribution of the FEV slopes among the Follow-Up Group is illustrated in Fig. 4.2, distinguishing between smokers and others. The relationship between smoking, FEV level, and FEV loss is discussed in Chapter 5; here, we merely note that there does appear to be something of a 'tail' of excessively steep FEV slopes, particularly in smokers. The single very steep slope in an ex-smoker was associated with the recurrence of asthma during our study (Chart F.3 in the Appendixes).

Vital capacity (VC)

Vital capacity (VC) was not measured until the sixth survey in January 1964. It was measured again in the summer of 1965 and in the last five surveys. The mean values in the 422 constant attenders who attended all these surveys and gave acceptable readings of VC are shown in Table 4.2 and Fig. 4.3. The biases of the various observers

Table 4.2. VC means and biases 1963–9

Mean values of VC at surveys 6, 9, and 13–17 in 422 men who gave acceptable readings at all of these surveys and individual observer biases at these surveys

Survey	Year	Mean VC (litres)	Individual observer biases†
6	1963–4	4·438	+34, −8, −28, −36
9	1965	4·295	+33, −20, −22
13	1967	4·160	+50, −12
14	1967–8	4·094	+112, +109, +5, −81
15	1968	4·206	+9, −8, −22
16	1968–9	4·132	+49, +30, −1, −33
17	1969	4·182	+11, −8, −25

† See Appendixes, section B.2.

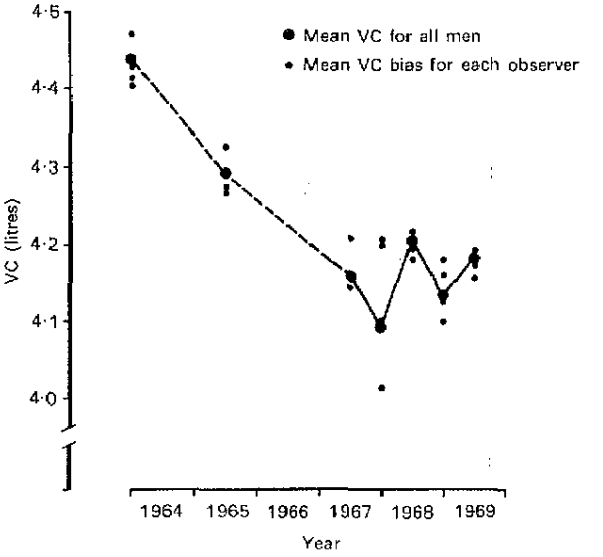


Fig. 4.3. VC means and biases

Mean VC at surveys 6, 9, and 13–17 for 422 men who gave acceptable VC readings at all of these surveys, with mean observer biases.

at each survey, estimated as in section B.2 of the Appendixes, are also given. There appears to have been a fall of some 300 ml between 1964 and 1967. Thereafter the level remained constant with slightly higher values in summer than in winter. These observations are difficult to interpret unless the relatively high values before 1967 were due to some undetected technical error. Since no tracings of the expirations were kept, this cannot now be investigated. As described

in section B.4 of the Appendixes, individual rates of change of VC were estimated for each man, but for the reasons there given these are not considered reliable enough to be of much interest.

Smoking habits

These are described in Table 4.3 and Fig. 4.4, both of which have been corrected to estimate (Appendixes, section B.7) what would have been observed had the 1961 sample been a random one. At the initial survey, 72 per cent were smokers, which corresponds closely with the national average in that year (Todd 1972). After the initial survey, about 5 per cent of the smokers gave up, perhaps because of the psychological effects of our study, and the overall mean cigarette consumption decreased by about 13 per cent. This is rather more than the general fall of about 5 per cent in cigarette consumption which followed publication of the first report of the Royal College of Physicians on Smoking and Health in 1962. Although reporting biases in assessing *whether* men smoke are unlikely to change much with repeated questioning, it is possible that reporting biases in assessing the *number* of cigarettes smoked per day might change with repeated questioning. We therefore record that reported consumption per smoker was about 8 per cent higher at the initial survey, but we do not know if the actual consumption then was any different. A very slight decline in the proportions of current smokers and in the mean cigarette consumption continued to occur between 1962 and 1969, interrupted only by a slight temporary increase in 1966.

The 1960s was the decade during which the majority of British cigarette smokers began to use filter-tips, and it is not surprising to find that the proportion of cigarette smokers in our Follow-Up Group who used filter-tips increased from 25 per cent in 1961 to 50 per cent in 1969; if anything, the change in our men seems to have been less rapid than the change in the general population, in which 19 per cent and 75 per cent of cigarette tobacco was smoked with filter-tips in 1961 and 1969 respectively (Todd 1972). However, our Follow-Up Group differs systematically in age, sex, geographical location, and social class from a random sample of British smokers, and we have described the proportion of smokers† using filter-tips rather than the proportion of cigarette tobacco smoked with filter-tips. Given these limitations, the pattern of changes of filter-tip usage that we have observed does not differ sufficiently markedly from the national pattern of change to disquiet us, although it is somewhat surprising

† Although we gave each cigarette smoker a score of 0, 25, 75, or 100 per cent according to whether he used filter-tips none, less than half, more than half, or all of the time, the large majority of these assigned scores were either 0 per cent or 100 per cent.

Table 4.3. Smoking habits 1961–9

Changes in mean smoking habits observed in the Follow-Up Group at summer surveys 1961–9, corrected for 1961 stratification

Summer	Percentage of current smokers	Mean daily cigarette consumption, all men	Mean percentage filter-tip usage, cigarette smokers only
1961	72	9·6	26
1962	68	8·3	27
1963	68	8·4	32
1964	67	8·4	32
1965	67	7·9	40
1966	69	8·7	42
1967	67	8·1	42
1968	66	8·0	46
1969	64	7·9	50
Approximate S.E. of each value	±2	±0·4	±3

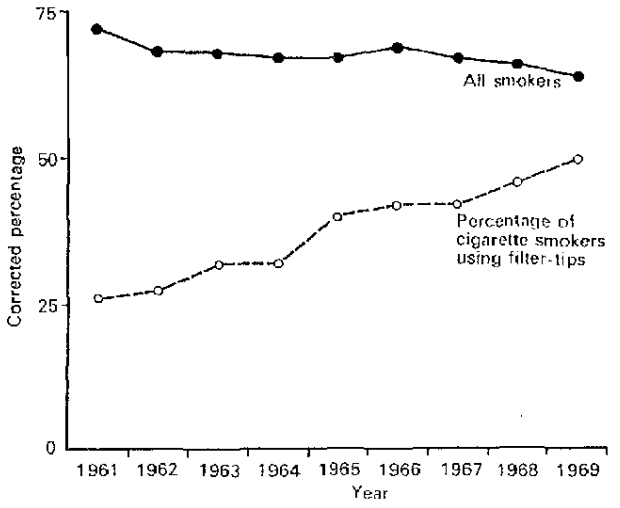


Fig. 4.4. Smoking habits 1961–9

Summer surveys, 1961–9: Follow-Up Group corrected for 1961 stratification: percentages of smokers of any form of tobacco, and percentage of cigarette smokers who used filter-tips.

that we observed as many as 25 per cent filter-tip users in summer 1961.

Mucus hypersecretion

Surveys of British men, including our own initial (1961) survey, usually show a higher prevalence of mucus hypersecretion in older

subjects. Our age gradient was not marked (Tables 3.7 and 3.8, both on p. 42), but even this small age gradient (if it existed because mucus hypersecretion increases during adult life rather than as a cohort effect) suggested that mean sputum volume and mean phlegm score should each increase by about 10 per cent during the eight-year course of our study, and such an increase should be detectable by our methods. However, the mean values of our indices of mucus hypersecretion actually declined during the course of our study (Table 4.4; Fig. 4.5). It is of some interest to know whether this observed decline is real or artefactual and, if real, what the causes of it might be.

The main possible artefact in the phlegm questionnaire results is due to a change in the question, from 'each year' at the 1961 survey (Appendixes, section A.3) to 'last winter' at subsequent summer surveys (Appendixes, section A.4). A minor artefact in the pattern of phlegm questionnaire results is that survey 2 was a winter survey, while all other surveys at which phlegm questions were asked were summer surveys. Another influence is that between 1961 and 1962 the percentage of our men who smoked decreased by about 10 per cent. It is also possible that, as the men learned that phlegm production would be enquired about regularly, they began to observe and report their phlegm production more accurately. Moreover, men might become bored with spitting into bottles and therefore less co-operative (Freedman *et al.* 1972).

Apart from the effects of learning and of the progressive failure to co-operate with morning expectoration and return of the sputum bottle, two further biases affected our sputum volume assessments. First, the collection technique at the first five surveys differed from that at subsequent surveys in that men were given one bottle at the initial survey, three bottles to be used on successive mornings immediately after surveys 2–5, and three bottles to be filled at weekly intervals after surveys 6–17. It is possible that the degree of co-operation in filling bottles immediately after the survey would be greater than that in filling bottles weeks later. Because of this, neither mean sputum volumes nor proportions of non-empty sets of bottles at surveys 1, 2–5, or 6–17 can be directly compared with each other.

Secondly, the sputum volume measurements at surveys 10–17 were biased upwards by an indeterminate amount. This occurred because in 1966 we started to use plastic bottles for the sputum instead of glass ones, and the standard bottles, by comparison with which the volume in each non-empty sputum bottle was assessed, lost about 0·5 ml† during the course of each of these surveys by

† Estimated by subsequent experiment.

Table 4.4. Expectoration 1961–9

Changes during 1961 to 1969 in mean values recorded in the Follow-Up Group of various indices of mucus hypersecretion, corrected for 1961 stratification. (Values that may be particularly biased appear in brackets; see text.)

Time	Survey No.	Mean 0–4 phlegm score	Percentage of non-empty sets of sputum bottles‡	Mean volume of sputum recorded per bottle (ml)‡
S 1961	1	(1·15)	(33)	(1·08)
W	2	(1·12)†	46	1·04
S 1962	3	1·06	33	0·66
W	4	—†	38	0·96
S 1963	5	0·80	29	0·64
			Change to weekly bottles	
W	6	—†	33	0·73
S 1964	7	0·91	26	0·62
W	8	—†	33	0·79
S 1965	9	0·80	25	0·52
W	10	—†	30	0·53
S 1966	11	0·85	24	0·55
W	No survey	—	—	
S 1967	13	0·73	25	(0·63)
W	14	—†	32	(0·83)
S 1968	15	0·92	29	(0·78)
W	16	—†	31	(0·82)
S 1969	17	0·73	27	(0·70)
Approximate S.E. of each value		±0·06	±2	±0·08

† Phlegm questionnaire not administered at winter surveys except 1962.
‡ Excluding from each survey men who returned no bottles then.

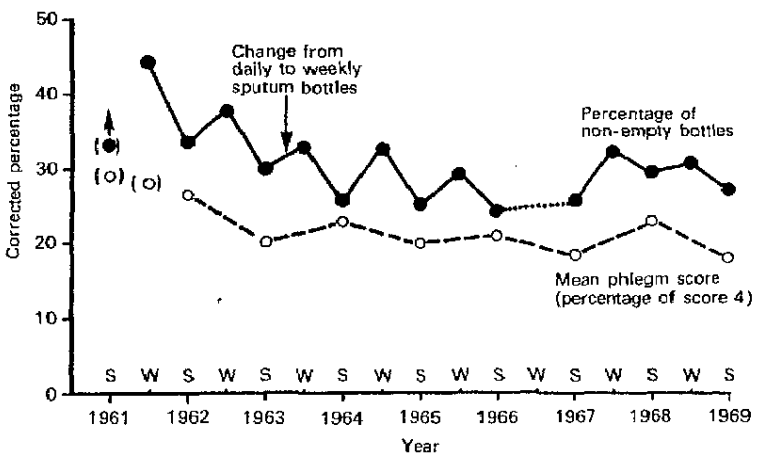


Fig. 4.5. Expectoration 1961–9

Expectoration in the Follow-Up Group 1961–9, corrected for 1961 stratification, from Table 4.4. Bracketed points may be biased: see text.

transpiration through the plastic. This must have caused an average over-estimation of the volume in non-empty bottles of about 0·3 ml, with a consequent over-estimation of the overall mean sputum volume at those surveys of about 0·1 ml. This bias would affect recorded volume, but not whether or not the bottle is recorded as empty. Because of this, and because the mean sputum volume may be more critically dependent on learning and co-operation than the proportion of non-empty bottles is, we feel that trends in mucus hypersecretion are likely to be better described by the proportions of non-empty bottles at surveys 6–17 than by the means of the sputum volumes at those surveys. (This is confirmed by the observation (Fletcher *et al.* 1974) that, among men with the same proportion of non-empty bottles, there was no correlation between mean sputum volume and either FEV or chest episode frequency.)

Because of biases in mean phlegm scores and sputum bottle results due to changes in technique and learning effects, especially during the first two years of our study, it is impossible to establish from our data whether a secular decrease in chronic mucus hypersecretion did occur in our population during the 1960s.

To help us decide whether a secular decrease really did occur, the men who attended survey 13 in the summer of 1967 were asked: 'Since we first saw you six years ago, do you think there has been any change in the quantity of phlegm you bring up on most days first thing in the morning?' Those who replied 'Yes' were asked whether there was now *definitely* less or more phlegm: 562 men replied that there had been no definite change; 22 (3·5 per cent) said they now definitely had more phlegm; while 50 (7·8 per cent) said they definitely had less. A question requiring recollection over a six-year period is inevitably inaccurate, but the replies were consistent with a downward trend of mucus hypersecretion. Some further evidence that the decline of mucus hypersecretion was real may be derived from the survey conducted in 1959 on a random sample of all men at the London Transport Workshops (Fletcher and Tinker 1961). Although the techniques of sputum volume measurement were not the same as in the 1961 survey, the proportions of empty and non-empty bottles are comparable, and 229/462 (50 per cent) of the 1959 bottles were non-empty, as compared with only 38·6 per cent of the 1961 bottles (Table 3.8, p. 42). This indicates that a decline in sputum volume may already have begun before 1961.

There are various possible causes for such a decline in expectoration if it did indeed occur. First, there was a great decrease in air pollution in London, especially in the years immediately preceding our study (Fig. 4.6). Secondly, our men cut their smoking down

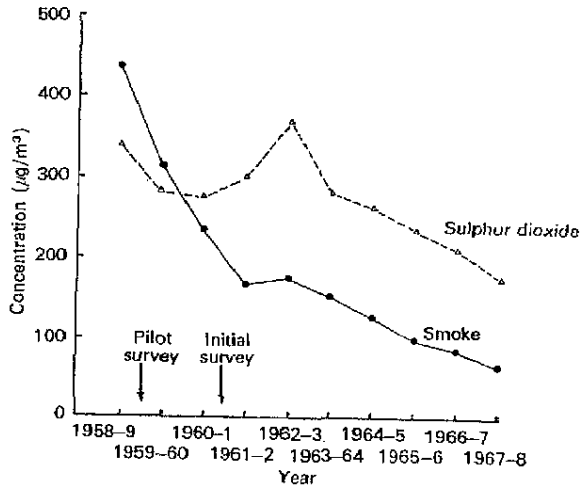


Fig. 4.6. Air pollution 1958–68

Mean concentration of black smoke and sulphur dioxide at seven sites in Central London, October–March (from data supplied by Mr. R. Waller).

more than the average in the United Kingdom over the same period. Thirdly, there was the increasing use of filter-tipped cigarettes by smokers—but we found no correlation of filter-tip usage with any of our indices of expectoration (Table 6.7, p. 117). Next, there was a decrease in the average tar delivery of popular brands of cigarettes over the duration of the study, but we have no direct evidence of any possible effect that this may have had for we did not assess it in individual men. Finally, there was probably an increase in the use of antibiotics for respiratory infections in the course of the study, since the total number of antibiotic prescriptions in Britain rose from 20 million in 1962 to 36 million in 1968 (National Economic Development Office 1972) but, since we shall conclude that chronic expectoration is not greatly affected by clinical respiratory infections, this may be of little relevance to trends in expectoration.

Indices of infection

Our two main indices of infection are the replies to our questions about chest colds and illnesses, and our assessments of sputum purulence. The obvious drawback of sputum purulence is that it cannot be measured in those without any sputum, and since only about a third of the men at any particular survey did produce

Table 4.5. Infective events 1961–9

Frequency among the Follow-Up Group, corrected for the 1961 stratification, of chest illnesses with phlegm, chest episodes, and purulent sputum

Time	Survey No.	Percentage of non-empty bottles with purulent sputum (grade ⩾3)	Percentage of men reporting, from previous six months	
			(a) Chest illness with phlegm (⩾1 week in bed)	(b) Chest episode (chest cold with phlegm or chest illness with phlegm)
S 1961	1	—	—	—
W	2	—	—	—
S 1962	3	10·4	1·2	14·6
W	4	19·1	2·0	21·3
S 1963	5	9·0	0·8	13·6
W	6	19·1	1·3	22·3
S 1964	7	16·3	0·6	13·6
W	8	14·5	1·1	20·0
S 1965	9	15·2	1·5	17·8
W	10	16·4	1·9	22·4
S 1966	11	6·0	2·6	14·1
W	No survey	—	—	—
S 1967	13	7·9	2·4	16·6
W	14	10·5	2·4	22·8
S 1968	15	9·2	3·3	20·2
W	16	13·5	2·1	21·1
S 1969	17	14·8	2·4	18·2
Approximate S.E. of each value		±2·8	±0·6	±1·7

sputum, this drawback is extremely serious, and prevents us being able to disentangle infection, as assessed by sputum purulence, from hypersecretion.

At the first two surveys, the questions asked about chest illnesses and colds were different from those asked subsequently so these early results cannot be compared with those obtained at later surveys. Table 4.5 and Fig. 4.7 give, for the men in the Follow-Up Group, corrected for the 1961 stratification, the frequency of chest illnesses (which by definition required a week or more in bed) with increased phlegm, chest episodes (which by definition involved increased phlegm), and purulent sputum among those who returned non-empty bottles. The erratic behaviour of purulence frequency is disquieting. Although assessment of purulence is prone to severe observer error between untrained observers, this can be corrected by training (Miller and Jones 1963). The four observers who carried out these assessments in the course of our study were all trained in the original technique and no change of observers coincided with the very marked

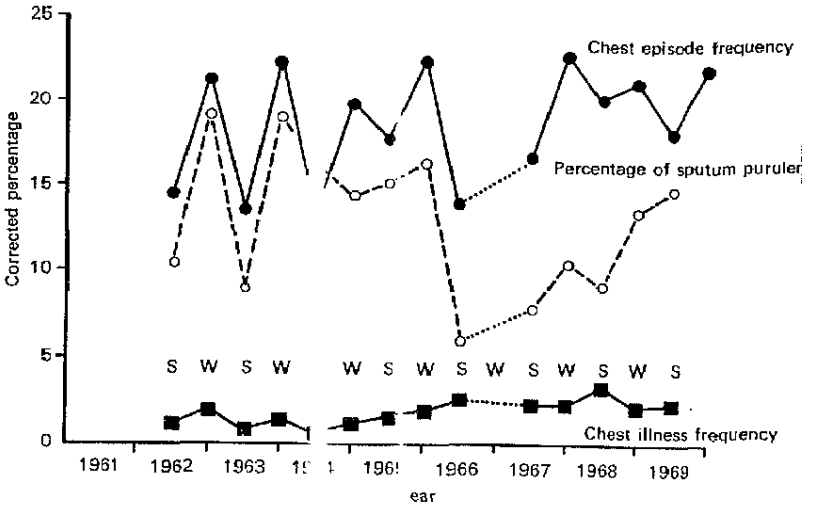


Fig. 4.7. ıfecti·e events 1962–9

Percentage frequency 1962–9 am ıg the Follow-Up Group, corrected for the 19 stratification, of chest illnesses with hlegm, chest episodes, and purulence (from Table 4.5

fluctuation in 1966. Moreo er, after the study had been completed we found good agreeme in assessments of purulence in 13 specimens of sputum betwe n the observer who did most of the late assessments and one of th origi al observers (section E.3 of th Appendixes). Nevertheless systematic observer error could still be responsible for the irregu ır trend of purulence frequency and perhaps, for its apparent ter lency to decline during the course of the study. This possibility cast further doubt on the value of sputum purulence as an index of br nchial infection.

The 'chest illnesses witl increased phlegm', which were distinguished from 'chest episode by necessitating a week or more in bed, are twice as frequent in th second half of the study (2·4 per cent per six-monthly survey) as n the first half (1·2 per cent), perhaps because of the increased e e of obtaining sickness benefits which existed later in the study. Be ause of this, the only index of bronchial infection in which we f l much confidence is chest-episode frequency: a clear winter/su mmer gradient is evident in every year, and a fairly constant rate of porting throughout the study indicates that no substantial learning effects determined the replies to these questions.

Although it is clear that v have observed something consistently

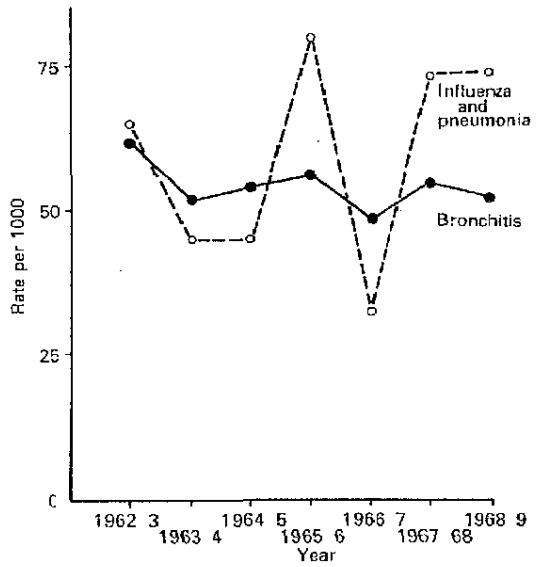


Fig. 4.8. National sickness rates 1962–9

Sickness absence rates 1962–9 per 1000 (June–May) for UK males aged 30–64 for incapacitating new spells of bronchitis and of influenza and pneumonia.

in our recording of chest episodes, it is not clear what sicknesses a random sample of these chest episodes would reveal. The special study of infective events which was made in 1962 suggests that the majority were the sort of sickness which would usually be described as 'an attack of bronchitis', rather than influenza or a head cold. In confirmation of this, the sickness absence returns for incapacitating new spells of 'influenza and pneumonia' (Fig. 4.8) show marked fluctuations which are not reflected at all in our chest episode frequencies, while the returns for incapacitating new spells of 'bronchitis' do not fluctuate much.

Dependence of the main indices on age

Finally, in order to characterize the main indices we abstracted from our prospective study in one further respect, we have, in Table 4.6, tabulated the way in which each depends on age among the 792 men who continued to attend sufficiently regularly to qualify for the Follow-Up Group. We do not intend any particular medical inferences to be drawn now from Table 4.6; it merely exists to be referred back to later on by readers who wish to do so when con-

Table 4.6. Age distribution of 1961–9 data

Each line describes the way in which one of our major indices depends on age. After the regression coefficient on age and its S.E., the mean and standard deviation in each group is given. The mean values in this table have been corrected (Appendixes, section B.7) to estimate what would have been observed in the Follow-Up Group if the 1961 sample had been random rather than stratified, but the standard deviations have not been thus corrected as it might have made them unduly inaccurate. In this table, H denotes the standing height.

Regression coefficient on age (±S.E.)	Age in 1961 30–39 (161 men, mean age 40·3 in mid-1965) (mean ±S.D.)	Age in 1961 40–49 (319 men, mean age 49·0 in mid-1965) (mean ±S.D.)	Age in 1961 50–59 (312 men, mean age 58·9 in mid-1965) (mean ±S.D.)	All men in the Follow-Up Group (792 men, mean age 51·1 in mid-1965) (mean ±S.D.)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
(or, given H, −0·047)				
FEV/H^3 (cl/m^3) 1961–9	−0·843 ±0·057	70·1 ±10·5	64·2 ±12·3	56·1 ±12·3	62·1 ±13·3
Maximal VC (litres) 1963–9	−0·048 ±0·003	4·86 ±0·74	4·62 ±0·69	4·01 ±0·74	4·43 ±0·79
(or, given H, −0·037)				
FEV^0/VC	−0·456 ±0·046	73·0 ±8·0	71·5 ±9·7	68·3 ±10·1	70·9 ±10·0
FEV slope (ml year) 1961–9	−0·53 ±0·14	−39 ±26	−45 ±28	−48 ±30	−45 ±29
(or, given FEV/H^3, +0·10)				
Mean daily cigarette consumption 1961–9	0·05 ±0·04	7·4 ±9·2	8·3 ±8·5	8·9 ±9·2	8·4 ±8·9
Chest episode frequency (per cent/survey) 1962–9	0·1 ±0·1	16 ±22	19 ±22	20 ±24	19 ±23
Mean 0–4 phlegm questionnaire score 1962–9	0·016 ±0·066	0·76 ±1·22	0·85 ±1·36	0·95 ±1·32	0·88 ±1·32
(or, given smoking habits, 0·013)				
Mean sputum volume (ml) 1962–9 at surveys when bottles were returned	0·027 ±0·008	0·58 ±1·85	0·62 ±1·31	0·89 ±1·95	0·72 ±1·71
(or, given smoking habits, 0·025)				

Table 4.7. Age distribution of FEV/H^3 in the Follow-Up Group

The numbers of men given in each cell are biased by the stratification of our 1961 sample, which will have slightly increased the proportion of obstructed men, and by the selective loss, by retirement or death before 1961 or by death between 1961 and 1967, of men whose mean FEV/H^3 1961–9 would have been less than 30 cl/m^3.

Age in 1961	Mean age in mid-1965	1961–9 mean FEV/H^3 in cl/m^3						All FEV/H^3
		<30	30–40	40–50	50–60	60–70	>70	
30–39 (10 years)	40·3	0	0	7	17	55	82	161
40–44	46·3	3	2	13	27	48	63	156
45–49	51·6	1	8	17	55	52	30	163
50–54	56·5	3	9	22	54	50	17	155
55–59	61·3	10	18	39	55	29	6	157
All ages	51·1	17	37	98	208	234	198	792
Percentage of all men		2	5	12	26	30	25	100

† In a man of height 1·71 m, FEV in litres may be obtained by dividing FEV/H^3 (cl/m^3) by 20.

sidering multiple regressions given age in Chapters 5 and 6. Tabl
4·7 gives extra detail for the particular case of FEV/H^3 (H being th
standing height), which is an index we shall subsequently mak
extensive use of.

5 Factors related to the development of airflow obstruction

Summary

THIS CHAPTER is the heart of the book. The correlation between smoking and more rapid loss of FEV has the characteristics of a causal relationship, because after allowing for age and present FEV there is a tendency for subsequent FEV losses to be greater in smokers than in ex-smokers. However, the correlations between either mucus hypersecretion or infective episodes (assessed in various ways) and more rapid loss of FEV do not have the characteristics of causal relationships, because after allowing for age and present FEV there is no relationship of either of them with FEV slope. Moreover, when an individual has more expectoration than his average, or when he suffers an infective episode, he does not suffer a greater loss of FEV than he suffers at other times.

Further examination of the relationship between smoking habits and changes in the FEV shows that, as expected, most smokers suffer very little loss of FEV as a result of their smoking, but that a minority (larger in heavier smokers) suffer substantial damage. Stopping smoking has, of course, little effect on those who have not been much affected by it, and even among the 'susceptible' minority stopping smoking does not allow lost FEV to be recovered. However, it does seem that among the 'susceptible' smokers the rate of loss of FEV is approximately halved after stopping smoking, reverting to a normal rate of loss and presumably considerably increasing their expectation of active life.

The observed relationship between low FEV and expectoration appears to exist chiefly because certain men have a special susceptibility, determined genetically or in early life, which predisposes both to expectoration and to more rapid FEV loss.

Introduction

We devote this chapter to a full analysis of which factors do and which do not affect the rate of decline of FEV in the Follow-Up Group. Severe reduction of FEV is necessarily disabling. Mucus

hypersecretion and recurrent bronchial infections in men normal FEV may be troublesome, and certainly cause a great of sickness absence, but they are not seriously disabling ur FEV is greatly reduced and are therefore of less practical sequence.

We shall first consider the analytical problems of finding whic the factors related to reduced FEV may be actual causes of F loss. In the light of this, we shall then examine those factors (smo habits, recurrent chest illnesses, and chronic phlegm product which have been shown to be related to reduced FEV in n prevalence studies, including our own initial survey (Chapter Lastly, we shall consider a number of other factors which have been suggested as possible causes of the development of chr airflow obstruction. Since men who had any condition which m have caused severe restrictive reduction of FEV (3 per cent of n see Appendixes, section B.4) were excluded from the Follow- Group, reduced FEV levels may be assumed to be chiefly ca by airflow obstruction, due either to changes in the airways o emphysema, and increased rates of decline of FEV (steeper F slopes) indicate more rapid development of these conditions. T the two terms 'reduced FEV' and 'airflow obstruction' are use this chapter almost interchangeably. We are, of course, aware differences of physique and main airways size also affect FEV, we are concerned only with abnormal reduction of FEV, and is determined predominantly by airflow obstruction.

Analytical problems: the horse-racing effect

Data such as ours, which cover only a relatively short fraction the lifespan of the men who took part in our study, present interest analytical problems. Associations had been observed between FEV and smoking, recurrent chest infections, and mucus hyp secretion in many prevalence studies. We intended to discover wh of these three associations arose because the factor concerned actu caused permanent loss of FEV, and which arose for other reaso We originally hoped to answer these questions merely by survey a group of men for a number of years, noting the losses in F which those men suffered over the course (1961–9) of our stu and then finding which of the three main factors of interest (smoki chest illnesses, and mucus hypersecretion) were correlated with FEV losses which occurred over this relatively short period. gradually came to realize, however, that this approach would help us to decide which factors were causing FEV loss and wh

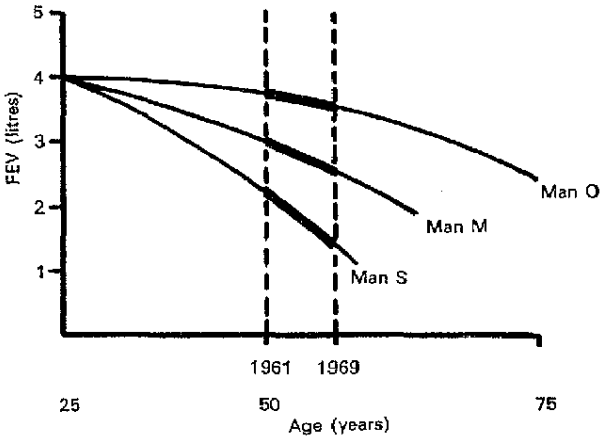


Fig. 5.1. Rapid loss causing low FEV and steep FEV slope

Graphs of FEV against age for three hypothetical men, all born in 1911, and all with an FEV of 4 litres at age 25. Man S develops severe airflow obstruction, man O develops very little, and man M develops moderate obstruction. The heavy lines indicate the FEV regression lines we would find in these men during our study (1961–9).

were not. The reasons why have some general interest, and are discussed in detail in section B.10 of the Appendixes. The parts of section B.10 which are essential for understanding our analysis of the causes of permanent loss of FEV are summarized here.

FEV loss is a gradual process (Appendix C) which accelerates slightly (Appendixes, section B.9) throughout adult life. It is clear that, for a mixture of constitutional and environmental reasons, some men lose FEV much more rapidly than others (Fig. 5.1). These 'FEV losers' will, of course, tend to have steeper FEV slopes and, by middle age, lower FEV levels. In the general population low FEV and rapid loss of FEV therefore tend to be correlated with each other, and a low FEV in middle age indicates an 'FEV loser'. Although there is no reason to suppose that low FEV *causes* steeper FEV slope, knowledge of a middle-aged man's FEV can thus help us to *predict* his FEV slope.

Anything associated with low FEV will thus automatically tend to be associated with FEV slope, whether or not it is an actual cause of FEV loss. However, a cause of FEV loss will usually (unless it operates absolutely constantly throughout life) tend to be associated with FEV slope, given what sort of 'FEV loser' each man is, while something that is not a cause may not be.

We can get some idea of what sort of an FEV loser each man is by comparing his FEV with that expected for his age and height, so, writing H for height, *factors which vary during adult life but which are not correlated with FEV slope, given FEV/H^3* (Appendixes, section B.6) *and age, are not significant causes of permanent loss of FEV*. In other words, most factors which are not correlated with FEV slope in a population of men all with the same height, age, and FEV level cannot be causes of FEV loss.

It is convenient to have a name for the process whereby FEV slope inevitably tends to be correlated with FEV level and thus with any factor which is correlated with the amount of FEV which has already been lost, and we call it the *horse-racing effect*. (This is because, when we were deciding that the observed correlation of steep FEV slope with low FEV level did not necessarily indicate that low level somehow caused steep slope, an analogy with a horse-race proved helpful: it is obvious that in a horse-race the fastest horses are out in front because their speed has put them there, not because being in front makes them 'speedy'.)

Multiple regressions, F-ratios, and correlation coefficients

In many subsequent tables we give quantitative correlations of FEV slope and level with all the factors we studied. Each cell in these tables describes a regression, giving the regression coefficient and the F-ratio. The regression coefficient in the correlation of FEV with some other quantity is an estimate of the difference between the average FEV of two groups of men whose values for the other quantity differ by one unit. For instance, in the case of a 0/1 quantity which is 1 for men who reported having had a chest illness and 0 otherwise, the regression coefficient of FEV on this 0/1 quantity equals the difference between the average FEV of men who did report at least one such illness and the average FEV of those who did not. For quantitative variables, the regression coefficient is based on their units of measurement. Thus, for sputum volume, measured in millilitres, the regression coefficient of FEV on sputum volume indicates the mean difference of FEV between groups of men differing by 1 ml in their sputum volume. These regression coefficients inevitably suffer from random variation. Since the variance of each regression coefficient can be estimated, it is possible to test whether any particular regression coefficient differs significantly from zero, or whether it is compatible with there actually being no relationship between the quantities being correlated.

The ratio of the square of the regression coefficient to its variance

Table 5.1. The interpretation of F-ratios

Approximate significance of F-ratios derived from regressions on single explanatory variables

Regression coefficient	Approximate F-ratio	Approximate statistical significance level	Approximate correlation coefficient
Less than 2 S.D.s from 0	< 4	Not significant ($0.05 < P$)	$\rho < 0.08$
Between 2 and 2·6 S.D.s from 0	> 4 < 7	$0.01 < P < 0.05$	$\rho \cong 0.09$
Between 2·6 and 3·2 S.D.s from 0	> 7 < 11	$0.001 < P < 0.01$	$\rho \cong 0.11$
Greater than 3·2 S.D.s from 0	> 11	$P < 0.001$	$\rho > 0.12$
5·5 S.D.s from 0	30	Infinitesimal	$\rho = 0.20$
8·5 S.D.s from 0	72	Infinitesimal	$\rho = 0.30$
12 S.D.s from 0	144	Infinitesimal	$\rho = 0.40$
16 S.D.s from 0	256	Infinitesimal	$\rho = 0.50$

is called the 'F-ratio'.† Those who prefer correlation coefficients to F-ratios can obtain them, in our study, by dividing the square root of any F-ratio by about 30. For example, in Table 5.8, p. 87 the correlation coefficient of chest episode frequency with FEV/H^3 is about $\sqrt{(39{\cdot}0)}/30 \cong 0{\cdot}2$. The statistical significance of a regression coefficient is determined by the F-ratio approximately as in Table 5.1.

Small or moderate F-ratios should be used only as rough guides to significance levels, without paying too much attention to their exact values. In the course of analysing our data, several hundred such F-ratios were calculated. A few of the smaller F-ratios, therefore probably mask real correlations and some of the large F-ratios are probably, by chance, false indicators of a correlation where none exists. This is especially true when there is conflicting evidence, such as a correlation with FEV slope without any correlation with FEV level.

The causes and correlates of low FEV

The relationship between rapid FEV loss and low FEV

We shall first present the data on the two factors which have the most significant correlations with FEV slope: FEV level (whose correlation with slope is to be expected as a 'horse-racing effect') and smoking habits. These factors account, respectively, for about

† See Appendixes, section B.15 for a formal definition of which F-ratios were calculated, and for the treatment of regressions on several parameters.

12 per cent† and 5 per cent of th[illegible] variance of our FEV slopes. (About 50 per cent of the variance [illegible]f our FEV slopes is accounted for by measurement errors, whic[illegible] are not, of course, correlated with anything.)

In an earlier analysis of our findi[illegible]gs from 1961 to 1968 (Fletcher *et al.* 1970, 1972), we reported th[illegible] FEV slope was more closely correlated with the FEV as a perc[illegible]ntage of the slow vital capacity (VC) than with uncorrected FEV. [illegible]Although this is still true, the closeness of the correlation of FE[illegible]%VC (see p. 183) with FEV slope which we previously reported [illegible]s partly spurious owing to our having then derived mean FEV%[illegible]C only from those surveys at which both FEV and VC were me[illegible]ured. Since these were mostly in the latter part of the study, this i[illegible]roduced a factor of 'regression from the mean' (Appendixes, sectio[illegible] B.16), which is largely avoided by our present use of the ratio of [illegible]e weighted mean of all values of FEV to the highest reading of VC[illegible] (Appendixes, section B.6).

Since the VC itself may be severely [illegible]reduced in obstructive diseases, the ratio FEV%VC may be a relati[illegible]ely insensitive estimate of the severity of airflow obstruction eve[illegible] in men who have suffered considerable FEV loss since early ad[illegible]lt life, if they have also suffered a considerable reduction in their V[illegible]. We therefore also used the index FEV (in centilitres) divided b[illegible] H^3, the cube of the standing height in metres, to assess the s[illegible]verity of airflow obstruction (Appendixes, section B.6). Writing [illegible]is as FEV/H^3, we found that numerically FEV/H^3 in units of cel[illegible]ilitres per cubic metre (cl/m^3) was generally about 10 less than [illegible]he FEV%VC. The values of FEV%H^3 which divide our populati[illegible]n into three equal groups were roughly at 55 cl/m^3 and 65 cl/m^3 (co[illegible]pared with about 65 per cent and 75 per cent for the FEV%VC). [illegible]In other words, in a group of men (although not necessarily in [illegible]n individual man), FEV/H^3 (cl/m^3) is approximately equal to F[illegible]EV%VC − 10. Another way of keeping some feel for what differe[illegible]t FEV/H^3 values mean is to remember that in a man who is 1·7[illegible] m tall, FEV in litres may be obtained by dividing FEV/H^3 (cl/m^3[illegible] by 20.

The strong relationship shown in [illegible]Table 5.2 between FEV slope and either FEV/H^3 or FEV%VC s[illegible]ggests that both indices give reasonable estimates of previous FE[illegible]V loss. To correct for various biases (Appendixes, section B.3), th[illegible]e 'FEV slopes' are 15 ml/year steeper than simple regressions, so [illegible]hat their mean, −45 ml/year, equals the coefficient of age in the [illegible]gression of FEV on age and

† This corresponds to a correlation coefficient [illegible]0·35. This correlation coefficient would probably have been greater than 0·50 (Appendix[illegible] section B.11) if the FEV slopes had been estimated more accurately.

Table 5.2. Mean FEV slopes (ml/year) by FEV%VC and FEV/H^3

FEV%VC	FEV/H^3 (cl/m^3) <45	45–50	50–55	55–60	60–65	65–70	>70	All FEV/H^3
<60	−74 (72)	−49 (15)	−57 (14)	−42 (11)+	← (1)	(0)	(0)	−65 (113)
60–66	−55 (15)	−57 (25)	−44 (24)	−51 (24)	−48 (21)	−44 (8)+	← (4)	−50 (121)
67–75	→ (4)+	−49 (16)	−46 (36)	−45 (56)	−46 (58)	−36 (52)	−38 (64)	−42 (286)
>75	→ (1)+	→ (4)+	−39 (13)	−45 (30)	−44 (41)	−36 (53)	−35 (130)	−38 (272)
All	−70 (92)	−51 (60)	−46 (87)	−46 (121)	−45 (121)	−36 (113)	−37 (198)	must be −45 (792)

Where the numbers of men (which are given in brackets) are less than 10, adjacent FEV/H^3 cells have been pooled since the S.E. of a mean slope is about $\pm 28{\cdot}8/\sqrt{}$(no. of men). The arrows indicate the way in which small groups of men were combined with their neighbours. Thus, among men with FEV%VC > 75, one man with FEV/H^3 < 45 cl/m^3 and 4 men with FEV/H^3 45–50 cl/m were combined with 13 men with FEV 50–55 cl/m^3 to give a group of 18 men with FEV/H^3 < 55 cl/m^3 and mean slope −39 cl/m^3. No correction for the 1961 stratification has been performed since it does not bias the relationship between FEV slope and FEV level. The top left corner indicates where most obstructed men would be found.

height. (The validity of this is discussed on pp. 23 and 125. Standard errors and differences between FEV slopes are not affected by it.) Interpretation of Table 5.2 is simplified by the fact that since we find no correlation between FEV slope and age *given* FEV%VC or FEV/H^3, we may take the figures to apply fairly accurately to most middle-aged men (see Appendixes, section B.9). Almost all of the obstructed men will be near the top left corner of the table. The FEV, standardized for physique either by VC or by H^3, may therefore be useful in the identification of middle-aged men who, although still clinically well, have probably suffered substantial FEV loss already and who may therefore be expected to continue to suffer rapid loss unless effective preventive action can be taken.

Regression of FEV slope on FEV/H^3

The relationship between FEV/H^3 and FEV slope is shown in more detail in Fig. 5.2, which is a plot of them against each other for each of the 792 men in the Follow-Up Group, distinguishing between non-smokers, ex-smokers, and people who did smoke at one or more summer surveys. The apparently haphazard distribution of the data in Fig. 5.2 may be found surprising in view of the high statistical significance of the correlation between FEV slope and FEV level. This scatter arises both from the inaccuracies of FEV/H^3

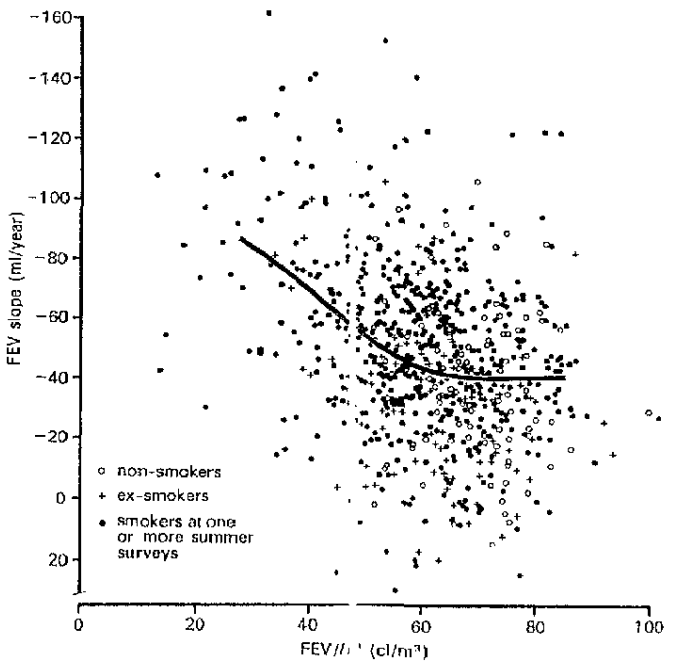


Fig. 5.2. FEV sl[illegible]pe by FEV/H^3

Relationship between FEV/H^3 and FEV slope [illegible] individual men in the Follow-Up Group. The quartic regression line of FEV slope on FEV/H^3 is also shown. Each FEV slope is the sum of the long-term rate of loss of FEV, a short-term deviation from this during the course of our study, and a measurement error. (The means and S.D.s of these are estimated in Appendix B to be about 45 ± 15 ml/year, 0 ± 5 ml/year, and 0 ± 20 ml/year respectively.)

as an index of past FEV loss and from short-term deviations and measurement errors that arise when FEV slope is assessed over a period as short as eight years. (Because of these errors, some of the steepest and most of the shallowest slopes are therefore probably too steep or too shallow: see Appendixes, section F.)

The regression line in Fig. 5.2 is almost flat among the healthy men whose FEV/H^3 is above 60 cl/m^3 (corresponding, in a man of height 1·71 m, to an FEV above 3 litres), while among men with lower FEV/H^3 the regression line is quite steep. This is because (Appendixes, section B.11) the long-term rate of loss of FEV has a very skewed distribution, so that, if we took a group of men, we would find that the shallow lifelong rates were all rather similar to each other, but that there was a wide spread among the steep lifelong rates. By middle age, the men with steep rates will tend to

have developed an FEV/H^3 below 60 cl/m^3, while the group with shallow rates will not. Among the men whose FEV/H^3 has remained above 60 cl/m^3, all the lifelong rates of loss of FEV are therefore rather similar to each other, and so there is not much of a horse-racing effect. Among these men, FEV/H^3 depends much more on physique than on past FEV losses and so FEV/H^3 is not strongly correlated with FEV slope. Among the men with FEV/H^3 below 60 cl/m^3, there are much greater differences between the lifelong rates of loss of FEV; FEV/H^3 is strongly determined by past FEV losses as well as by physique; and so FEV/H^3 is strongly correlated with FEV slope. (The likely behaviour of the regression line below 30 cl/m^3 is discussed in section B.9 of the Appendixes.) The relationship between FEV level and FEV slope is discussed further in section B.11, and appears to be of about the magnitude that would be expected if the long-term rates of loss of FEV had been operating on the FEV levels for about 25 years.

Smoking habits

The correlation of smoking habits with FEV slope is highly significant, and has characteristics compatible with a causal relationship (see p. 73 and Appendixes, section B.10), for it remains highly significant ($P < 0.001$) after adjusting for FEV/H^3 and age (Table 5.3). The effect of 'adjusting' FEV slope for FEV level in the middle column of Table 5.3 is to make the FEV slope shallower if the FEV is already low, which tends to be the case if the rate of loss of FEV earlier in adult life was rapid. Because of this, FEV slope 'adjusted' for FEV/H^3 and age no longer indicates the absolute rate of loss of FEV but, instead, it indicates whether FEV loss is now more or less rapid than it used to be. That part of the loss of FEV in smokers which is the result of previous smoking will thus tend to be abolished by adjustment for FEV/H^3 and age ('horse-racing effect'—see pp. 71–3). The simple average FEV slopes (Table 5.4) in various groups of smokers and the unadjusted correlations of smoking with FEV slope (Table 5.3, column 1) are therefore probably more relevant to the total effect of cigarette smoking on the rate of loss of FEV than are the adjusted correlations in Table 5.3, column 2.

Filter-tip usage appears to be without relevance to FEV level or slope. Lifetime smoking is not only, as might be expected, less relevant to the current rate of loss of FEV than current smoking is, but it is also, perhaps because of inaccuracy of recall (Todd 1966), no better correlated with FEV/H^3 than are current smoking habits. The significant excess of 46·8 over 29·0 (or of 61·1 over 44·0) in lines 4 and 1 of Table 5.3 shows that among the smokers the

Table 5.3. Multiple regression of FEV loss by smoking

F-ratios and significance levels generated by the regression analysis of the relevance of smoking habits to FEV and FEV slope, given age. (See section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios.)

	FEV slope given age	FEV slope given age and FEV/H^3	FEV/H^3 given age
F-ratio from dividing the men into 3 types of smoker: (a) non- or ex-smoker (b) light or variable (c) regular smoker	44·0 ÷ 2***	29·0 ÷ 2***	27·1 ÷ 2***
Difference between the mean among the non- or ex-smokers and the mean slope among the regular smokers	17 ml/year	14 ml/year	5·3 cl/m^3
Difference between the mean among the light or variable smokers and the mean among the regular smokers	5 ml/year	3 ml/year	2·9 cl/m^3
F-ratio from dividing the men into 9 types of smoker, as in Table 5.4	61·1 ÷ 8***	46·8 ÷ 8***	36·2 ÷ 8***
F-ratio for the mean proportion of filter-tips used, given amount and type of tobacco smoked in 1961–9	0·6	0·2	1·9
Regression coefficient on mean proportion of filter-tips used, given amount and type of smoking	3·2 ml/year	1·7 ml/year	2·3 cl/m^3
F-ratio for total lifetime smoking given 1961–9 amount and type	0·6	2·4	6·1
F-ratio for total lifetime smoking	9·1**	2·1	30·3***
Regression coefficient per 1000 packs of 20	−0·7 ml/year	−0·3 ml/year	−0·49 cl/m^3

** $P < 0.01$
*** $P < 0.001$

heterogeneity of mean FEV slope seen in Table 5.4 is statistically significant ($P < 0.01$). Speculation about the effects of smoking should, of course, be based on the mean values in Table 5.4 as these characterize the relationship more explicitly than the F-ratios in Table 5.3 do.

Further details of the quantitative relationship between FEV slope and smoking categories are given in Table 5.4. The mean slopes for non-smokers and for ex-smokers who stopped smoking before 1961 are essentially the same. This is in spite of the fact that the ex-

Table 5.4. FEV slope by mean smoking habits 1961–9 and FEV/H^3

FEV slope (ml/year ± S.E., which was estimated as $28{\cdot}8/\sqrt{n}$) by smoking categories and level of FEV/H^3. (Numbers of men n in brackets.) The 1961 stratification does not bias this table, except in the proportion of non-smokers, and it has therefore not been corrected for.

Smoking habits (see Appendixes, *section B.8*)	FEV/H^3 <55 cl/m^3	FEV/H^3 55–65 cl/m^3	FEV/H^3 >65 cl/m^3	All men in the Follow-Up *Group*	FEV/H^3 in this smoking category (cl/m^3)
Non-smokers	−36±9 (10)	−45±6 (25)	−33±3 (68)	−36±3 (103)	69
Ex-smokers 1961–9	−34±6 (25)	−36±5 (37)	−26±4 (42)	−31±3 (104)	62
Gave up in 1961–2	−37±11 (7)	−47±11 (7)	−26±14 (4)	−38±7 (18)	59
Pipe and/or cigar only	−74±12 (6)	−54±8 (12)	−37±8 (13)	−51±5 (31)	64
5 or less cigarettes/day	−45±5 (28)	−52±6 (20)	−39±4 (45)	−44±3 (93)	62
Irregular, >5/day	−73†±4 (45)	−37±5 (28)	−44±5 (40)	−54†±3 (113)	58
Regular, 5–15/day	−52†±4 (56)	−49±4 (59)	−39±4 (61)	−46†±2 (176)	59
Regular, 15–25/day	−70†±5 (39)	−51±4 (45)	−38±5 (31)	−54†±3 (115)	59
Regular, >25/day	−59†±6 (23)	−45±10 (9)	−52±11 (7)	−54†±5 (39)	55
All men	−57±2 (239)	−46±2 (242)	−37±2 (311)	must be −45 (792)	61

† Biased (see text); in men with FEV/H^3 <55 cl/m^3, the mean FEV slopes should be changed to −64 (irregulars), −55 (5–15 cigarettes/day), −74 cl/m^3 (15–25), and −63 cl/m^3 (25+), which will cause some slight changes in the overall mean slopes in these smoking categories.

smokers were on average four years older and had significantly lower mean FEV/H^3 than non-smokers. The small group of men who gave up smoking early in the study also have a mean slope that is slightly better than average. (It would have been better still if a single asthmatic with a very steep slope had not happened to be included in this group: see below.) Pipe and cigar smokers have a slightly greater mean rate of FEV decline than ex-smokers (see p. 85). The steepest rates of decline are those of regular cigarette smokers. There is an apparent dose–response effect in that heavy smokers (more than 15 cigarettes/day) have steeper FEV slopes than

lighter smokers (5–15 cigarettes/day), but among the heavy cigarette smokers there is no significant difference between those smoking more and those smoking less than 25 cigarettes/day. This may be because the cigarette smokers who had lower levels of FEV tended to cut down their cigarette consumption before the study more than did those with higher FEV levels (p. 82).

Unfortunately, the mean FEV slope of the obstructed irregular smokers in Table 5.4 is somewhat biased, and should really be 9 ml/year shallower, while the mean FEV slopes of the obstructed regular smokers should all be about 4 ml/year steeper. This bias arose because in 1968 we felt we ought to warn the obstructed cigarette smokers with the steepest FEV slopes that they should stop smoking. Eight of these men, with a mean FEV slope of −113 ml/year, did stop or change to pipes or cigars for one or both of the 1968 or 1969 summer surveys. Their steep FEV slopes in our study therefore caused us to change their smoking habits and thus to re-classify them as 'irregular smokers'. Classification of these eight men by their 1961–7 smoking habits is perhaps more appropriate. If this is done the mean FEV slopes and numbers of men in the obstructed irregulars, 5–15 regulars, 15–25 regulars, and 25+ regulars would become respectively −64 ml/year (37 men), −55 ml/year (58 men), −74 ml/year (43 men), and −63 ml/year (25 men), and the overall means in these four groups would be altered by +4, −1, −1, and −2 ml/year respectively. If the asthmatics were omitted from Table 5.4, the mean slope of the men who gave up in 1961–2 would be 6 ml/year shallower, and that of the irregular smokers would be a further 4 ml year shallower.

Effects of giving up smoking. The fact that smokers who stopped before 1961 and those who stopped in 1961–2 have FEV slopes similar to non-smokers, in spite of their FEV levels having been reduced by their previous smoking, is perhaps our most important finding. It suggests that further damage to FEV due to smoking ceases within at most a few years of stopping, but there is no evidence of recovery from damage already done (see p. 84).

The mean FEV/H^3 of the ex-smokers, adjusted to age 50 in 1965 by the regression coefficient (0·843 cl/m^3 per year) of FEV/H^3 on age, was 61·2 cl/m^3; the mean FEV/H^3 of the men smoking up to 15 cigarettes/day, adjusted similarly, was 59·4 cl/m^3. The mean duration of stopping smoking among the ex-smokers was about 11 years. For a man of height 172 cm, a difference of 1·8 cl/m^3 in 11 years represents an average loss of FEV of 8 ml/year. The actual difference between the mean slopes of the non-smokers and

Table 5.5. Changes in smoking by FEV%VC

Daily cigarette consumption among men seen in 1961 and 1969 who were smoking some cigarettes in 1961 and a different number in 1969, divided by FEV%VC.

1961 daily cigarette consumption	FEV%VC < 66⅔		FEV%VC > 66⅔	
	Fewer in 1969	More in 1969	Fewer in 1969	More in 1969
1–14	35 (70%)	15 (30%)	63 (52%)	58 (48%)
15+	50 (71%)	20 (29%)	79 (66%)	40 (34%)
All smokers†	85 (71%)	35 (29%)	142 (59%)	98 (41%)

†Test for difference of proportions: $\chi_1^2 = 4{\cdot}2$, $P < 0{\cdot}05$.

the men smoking less than 15 cigarettes/day is of this order (9 ml/year ±4), and the data are therefore compatible with the hypothesis that when (or a few years after) smoking stops, accelerated loss of FEV due to smoking ceases, but lost FEV is not recovered. The data are, however, far too imprecise for this to provide any strong confirmation of this hypothesis.

Since many men varied their cigarette consumption during the study, mean daily consumption was used to classify smoking habits. One possible explanation for the poor relationship between mean consumption and slope in the heavier smokers would be that the heavier smokers with lower average FEV levels and steeper slopes have tended to reduce their cigarette smoking in the past more than did similar smokers with higher FEV levels and less steep slopes. This tendency would reduce differences between mean FEV slopes in lighter and heavier smokers. A slight tendency for this to occur can be seen in Table 5.5, which shows that men with obstruction have a greater tendency to reduce their smoking than men without obstruction do. This is confirmed by a significant ($P < 0{\cdot}01$) correlation between 'cigarette regression' and FEV/H^3. (The 'cigarette regression' for each man is the average rate of change of his daily cigarette consumption from 1961 to 1969 (Appendixes, section B.4). The correlation between this and FEV/H^3 is very weak—during the whole study, the difference per litre of FEV would only be about 1 cigarette/day—but it does remain significant ($P < 0{\cdot}02$) after adjustment for age, smoking type, and average cigarette consumption from 1961 to 1969.)

The 'susceptible minority' of smokers. The mean effects of smoking on the rates of loss of FEV in Table 5.4 are so slight as to suggest

Table 5.6. FEV slopes by smoking habits in obstructed and in unobstructed men

Mean rates of change of FEV during the 1960s (ml/year), mean levels of FEV in 1965 (litres), and percentages of men with and without airflow obstruction (FEV%VC < 66⅔ and FEV/H^3 < 50 cl/m^3) by smoking habits during the 1960s. The data in this table have been corrected for the 1961 stratification. See Appendix G.1, p. 254 for age-standardized version.

	With airflow obstruction	Without airflow obstruction
103 lifelong non-smokers	None with obstruction (0%)	−36 ± 3 ml/year 3·6 litres (100%)
122 ex-smokers (gave up before 1962)	−36 ± 8 ml/year 2·2 litres (10%)	−32 ± 3 ml/year 3·3 litres (90%)
387 moderate smokers (average up to 15 cigarettes/day)	−63 ± 4 ml/year 2·0 litres (12%)	−44 ± 2 ml/year 3·3 litres (88%)
180 heavy smokers (average over 15 cigarettes/day)	−78 ± 6 ml/year 2·2 litres (26%)	−49 ± 3 ml/year 3·1 litres (74%)
792 men: all habits	−66 ± 3 ml/year 2·1 litres (13%)	−42 ± 1 ml/year 3·3 litres (87%)

that the effect of smoking would be of little practical consequence over three score years and ten. This is not true; the *mean* effects of smoking are small because most smokers suffer no substantial obstructive damage, but a minority suffer such severe obstructive damage that they are eventually disabled or killed by it. It might, in principle, be possible to tell, in middle age, whether a particular smoker is one of the unfortunate 'susceptible minority' or not by simply finding out whether his FEV has been severely reduced since early adult life. (The practical difficulties of this are discussed on p. 146.)

The effect of smoking on the 'susceptible minority'† can best be illustrated by examining the men in the top left-hand corner of Table 5.2, who have low FEV%VC and low FEV/H^3. The selective omission from our 1961 sample of 'asymptomatic' smokers could distort the relationship between smoking, FEV, and FEV slope, and we must estimate from our actual data the relationship between these three factors that would have been found had the 1961 sample been completely unstratified. This is done in Table 5.6, which indicates that about 13 per cent of a Follow-Up Group

†Of course, 'susceptibility' is unlikely to be an all-or-nothing attribute: in reality, a spectrum of susceptibility probably exists. However, our argument is most easily followed if it is presented in terms of two contrasting groups, the 'susceptibles', who in their normal lifespan may become disabled by obstructive disease if they smoke, and the 'non-susceptibles', who will not, whether they smoke or not.

derived from an unstratified sample would have been 'obstructed' (i.e. with FEV%VC $< 66\frac{2}{3}$ and FEV/$H^3 < 50$ cl/m^3, which corresponds to an FEV $< 2{\cdot}5$ litres in a man of height 1·71 m). In 1972, 7 per cent (21 032/300 389) of all male deaths in England and Wales were attributed to 'chronic bronchitis and emphysema' (ICD 491 and 492). To the extent to which FEV in middle age can predict who this 7 per cent of men that will die of these causes will be, a degree of obstruction so severe that only 13 per cent of a random sample have it is therefore quite likely to be prognostically significant.

Despite the fact that 103 of our Follow-Up Group were non-smokers, *none* of these 103 non-smokers were 'obstructed'. This confirms that nowadays real disablement is generally restricted to smokers and ex-smokers. Ten per cent of the pre-study ex-smokers were 'obstructed', showing that obstruction, once smoking has caused it, is not usually reversed even several years after smoking ceases. Twelve per cent of moderate smokers were obstructed, while 26 per cent of heavy cigarette smokers were obstructed.

The chief interest of Table 5.6, however, is not the various percentages obstructed, but rather the *rates* of loss of FEV that occurred. The group who were not obstructed consisted mainly of men who were not 'susceptible' to tobacco smoke, plus the non-smokers, some of whom might have become obstructed if they had been smokers. Among these non-susceptible men the number of cigarettes smoked per day had little effect, and, of course, nor did stopping smoking. However, among the susceptible men the amount smoked had a more marked effect—both groups of susceptible smokers lost FEV much more rapidly than normal, but the difference between them was 15 ml/year. These differences are discussed further in Chapter 7, and are illustrated by Fig. 7.1 on p. 130. Among the susceptible men there is also a very marked effect of stopping, which is encouraging for it suggests that even among *susceptible* smokers who have already suffered a considerable reduction in their FEV due to their smoking, the rate of progressive damage will slow to that typical of non-smokers (or non-susceptible smokers) if their exposure to tobacco smoke ceases.

Fig. 5.2 on p. 77 complements Table 5.6 in that, although the smoking habits are given in less detail, the FEV/H^3 and FEV slopes are given exactly. As already emphasized (p. 77), although the FEV/H^3 values are reasonably accurate, each FEV slope is subject to substantial random errors.

Table 5.7 lists the frequency of occurrence of extremely negative or positive FEV slopes by smoking habit. Since, however, individual

Table 5.7. Steep and shallow FEV slopes

This table gives the numbers of subjects with FEV slopes more than ±45 ml/year from the mean. Steep slopes are significantly ($P < 0{\cdot}001$) commoner among the smokers: see also Fig. 4.2 (p. 56).

	FEV slope steeper than 90 ml/year	FEV slope positive
103 lifelong non-smokers	2 (2%)	7 (7%)
122 ex-smokers (gave up before 1962)	2 (2%)	9 (7%)
387 moderate smokers (average up to 15 cigarettes/day)	27 (7%)	19 (5%)
180 heavy smokers (average over 15 cigarettes/day)	20 (11%)	5 (3%)
792 men: all habits	51	40

FEV slopes are subject to random measurement errors with a S.E. of over ±20 ml/year, some of these extreme slopes are probably spurious. The men with the most extreme slopes are described individually in section F.1 of the Appendixes.

The mean FEV slope of the 31 pipe and cigar smokers was steeper than that of the non-and ex-smokers and similar to that of the lighter cigarette smokers. Eighteen of these men had FEV/H^3 levels below 65 cl/m^3 and the small group with FEV/H^3 below 55 cl/m^3 had FEV slopes steeper than other groups of smokers with similar levels of FEV/H^3. By definition, the pipe and cigar smokers kept to the same smoking habit throughout the study, but 21 of them had previously smoked cigarettes. All but 4 of the 18 men with FEV/H^3 below 65 cl/m^3 and all of the small group with FEV/H^3 below 55 cl/m^3, were former cigarette smokers. It is possible that these former cigarette smokers changed to pipe smoking because of respiratory symptoms associated with an FEV level already reduced by cigarettes, but that this change of habit did not arrest their rapid decline of FEV. It has been reported (Castleden and Cole 1973) that when men change from cigarettes to pipes and cigars many of them continue to inhale as much as when they smoked cigarettes, but we did not ask whether this was true of the men in our study.

Bronchial infection

Lack of any independent relationship with FEV slope. Chest episode frequency assesses the frequency of symptomatic infections quite

accurately. Some other aspects of bronchial infection are assessed by sputum purulence or by *H. Influenzae* antibodies, but chronic low-grade bronchial infections will manifest themselves to us only by causing mucus expectoration, and these low-grade processes are therefore dealt with in Chapter 7, pp. 134–5 when we discuss hypersecretion.

In Table 5.8 we give the results of the multiple regression analyses, relating indices of bronchial infection to FEV and to FEV slope, which are needed to help decide whether the relationship between these variables could plausibly be one of cause and effect or not (see p. 72 and Appendixes, section B.10). To allow for the correlations between smoking, mucus hypersecretion, and bronchial infection which are reported in Chapter 6, some of the regressions in Table 5.8 are adjusted for smoking and some for both smoking and hypersecretion. When this is done, the correlations between bronchial infection and FEV/H^3 (adjusted for smoking) are very much weakened by adjustment for mucus hypersecretion, suggesting that the association of airflow obstruction with bronchial infection may arise principally because both are related to mucus hypersecretion. This means that the bronchial infections we assessed do not cause any permanent loss of FEV, and this is confirmed by the lack of any correlation at all between bronchial infection and FEV slope given age, FEV/H^3, and smoking. (The correlation with FEV slope given only age is a 'horse-racing' effect, equivalent to the correlation with FEV/H^3 itself.)

The differences between the strengths of the various correlations with FEV/H^3 in Table 5.8 are perhaps mainly due to differences in the accuracy with which the various indices assess bronchial infection, except for the strong correlation with purulence frequency. This latter correlation is, at least in part, an artefact which has arisen because measured purulence is automatically correlated with sputum volume, since a sputum bottle containing zero volume is automatically given a zero purulence rating (see p. 115).

The 'chest episode frequency' is a fairly accurate index, being an average calculated over many six-monthly surveys. Its relationship with age-standardized FEV/H^3 (SFEV/H^3) is described more fully in Table 5.9, which shows the extent to which men with low FEV report more frequent chest episodes (see also p. 110).

Independent confirmation of the non-causal role of symptomatic infections. The conclusion, based on the second column of Table 5.8, that the chest infections we assessed definitely do not cause permanent loss of FEV, can be *independently* confirmed by seeing

Table 5.8. Multiple regression of FEV loss by infection

F-ratios (and regression coefficients) arising from the relationships between FEV level, FEV slope, and various measures of the presence of bronchial infection. (See section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios.)

	FEV slope (ml/year) given age	FEV slope given age, FEV/H^3, and smoking habits	FEV/H^3 (cl/m^3) given age and smoking habits	FEV/H^3 (cl/m^3) given age, smoking habits, and phlegm†
Chest episode frequency (fraction of surveys 1962–9 with a chest illness or cold with increased phlegm reported from the previous 6 months)	10·7** (−15)	0·9 (−4)	39·0*** (−11·4)	11·0** (−6·7)
Usual chest cold When asked in 1961, did the subject claim to suffer a chest cold each winter? (0 = no, 1 = yes)	2·8 (−2)	0·3 (+1)	16·6*** (−4·2)	8·6** (−3·0)
Chest illness 1962–9 During the period of the whole study did the subject ever suffer a chest illness with increased phlegm requiring a week or more in bed? (0 = no, 1 = yes)	2·6 (−4)	0·1 (+1)	41·8*** (−6·5)	21·9*** (−4·7)
Chest illness 1958–61 In the 3 years before the first survey did the subject suffer a chest illness with increased phlegm requiring a week or more off work? (0 = no, 1 = yes)	1·1 (−1)	0·9 (+3)	10·3** (−3·7)	6·2* (−2·8)
H. Influenzae Antibodies found in the serum in 1968? (0 = no, 1 = yes, 0·29 = not tested in 1968)	4·7* (−6)	0·6 (−2)	2·6 (−1·7)	1·6 (−1·3)
Purulence frequency (fraction of surveys 1962–9 at which the mean purulence of the sputum specimens returned was 3 or more)	1·4 (−12)	2·4 (+15)	42·9‡*** (−25·7)	8·0** (−12·5)
Purulence presence (0 if the purulence frequency is zero, 1 otherwise)	1·8 (−3)	0·7 (+2)	34·0‡*** (−5·3)	4·0* (−2·1)

† Mean sputum volume 1962–9 and mean four-point phlegm score 1962–9.
‡ These correlations are artificially inflated by the necessary correlation between purulence measurement and sputum production.
* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

Table 5.9. Chest episodes by SFEV/H^3

Percentage distribution of chest episode frequency by age-standardized† FEV/H^3 (SFEV/H^3), corrected for the original stratification.

Chest episode frequency	SFEV/H^3 < 55 cl/m^3	SFEV/H^3 55–65 cl/m^3	SFEV/H^3 > 65 cl/m^3	All SFEV/H^3
No chest episodes from 1962 to 1969	22	32	31	30
0·1–19·9 per cent	26	28	36	31
20–39·9 per cent	25	26	21	24
40+ per cent	27	14	11	15
All men	100	100	100	100
Mean	26·1 ± 2·1	18·0 ± 1·5	15·7 ± 1·2	18·7 ± 0·9
Percentage of men in this SFEV/H^3 category	21·2	35·2	43·5	100·0

†The regression coefficient of FEV/H^3 is −0·843 cl/m^3 per year of age, so SFEV/H^3 = FEV/H^3 + 0·843 (age in 1965 − 50).

whether or not, for a particular group of men, their greatest FEV losses coincide with their infections. If a chest illness causes any permanent loss of FEV, the FEV observed at our various surveys should tend to show a decrease at the survey after the illness which does not recover at subsequent surveys. The ideal form of this pattern, in which no random errors in the FEV exist, is indicated in Fig. 5.3, where the FEVs at the surveys before and after an illness, together with the regression lines through them, are sketched. Although this pattern is idealized, the fact remains that if the illness has any effect on FEV (either temporary, affecting only one subsequent survey, as in Fig. 5.3(b), or permanent, as in Fig. 5.3(a)), the FEV at the survey at which the illness is reported (which is on average three months after the illness occurred) will tend to lie below the regression line.

Moreover, if the effect of the illness on the FEV is permanent *and* the two surveys preceding the illness were attended without an illness being then reported, the regression line will tend to be below the FEVs recorded at those two prior surveys. If this effect occurs, the residuals of the FEV readings about the regression line through them will tend to be positive just before the illness and negative at the survey at which the illness is reported. We have examined the relationship between the times of occurrence of chest illnesses (and of other indices of bronchial infection) to see whether any such relationship with the pattern of observed FEVs does exist, and it does not (Table 5.10).

Table 5.10 gives the mean FEV residual (column 1) at surveys where certain types of infective event were reported or found; it also gives the mean residuals (columns 2–4) at each of three

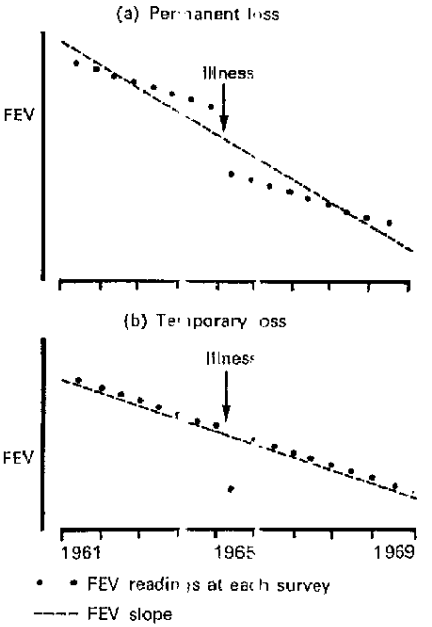


Fig. 5.3. FEV changes when events occur

To illustrate the effect on FEV slope and hence on residuals about the regression line of (a) permanent and (b) temporary reductions of FEV due to a chest illness.

successive surveys, in the instances where all three surveys were attended and the relevant event was not reported or found at the first two and then was at the last one. The S.E.s of the mean residuals in Table 5.10 are only approximate; no allowance was made in the calculation of them for the covariance between different residuals. (This affects the S.E.s in column 1 most strongly.) For this reason, the data in Table 5.10 should be regarded as merely descriptive rather than as a definitive analysis. For a definitive analysis, we need to fit the models

(a) chest illnesses have a permanent effect of unknown magnitude on FEV (as in Fig. 5.3(a)); and
(b) chest illnesses have a temporary effect of unknown magnitude on FEV (as in Fig. 5.3(b))

and estimate the unknown magnitudes by least squares (see Appendixes, section B.12). The least-squares estimates of the magnitudes of the temporary and permanent effects of various events are displayed in Table 5.11, together with their S.E.s. The advantage of the least-squares estimates is that, together with their

Table 5.10. FEV residuals when infective events occurred

Mean FEV residuals (ml ± approximate S.E.) about individual FEV regression lines in relation to certain infective events. (Numbers of FEV residuals contributing to each mean in brackets.) The effects suggested by this table are formally estimated in Table 5.11.

Nature of event	Mean FEV residual at all surveys when the event was present	Mean FEV residuals at 3 consecutive surveys which were all attended with the relevant event only present at the last one. (a) Event absent (12 months before event)	(b) Event absent (6 months before event)		(c) Event present
Chest illness with increased phlegm in the previous 6 months necessitating at least a week in bed	1 ± 9 (262)	−9 ± 13 (133)	12 ± 11 (133)	Illness between surveys b, c	5 ± 13 (133)
Chest cold with increased phlegm in the previous 6 months which did not necessitate a week in bed	−5 ± 3 (2198)	2 ± 6 (743)	−5 ± 5 (743)	Chest cold between surveys b, c	−5 ± 5 (743)
Purulent sputum (mean purulence score of all bottles returned at one survey being 3 or more)	−3 ± 7 (451)	−5 ± 10 (244)	−14 ± 9 (244)		−11 ± 10 (244) Purulent
H. Influenzae antibodies in the serum (assayed only in 1968)	5 ± 9 (178)	21 ± 11 (137) Antibodies not measured	−11 ± 11 (137) Antibodies not measured		2 ± 11 (137) Antibodies present

Table 5.11. FEV changes at the times of infective events

Limits imposed by our data on the biggest possible effects (permanent or temporary) of various infective events on the FEV (ml). Least-squares estimates based on the differences within particular men of the FEV changes when various events occur from the FEV changes at other times, calculated as described in section B.12 of the Appendixes.

Event reported or found	Least-squares estimate of the permanent effect of the event on the FEV (ml ± S.E.)	The permanent effect is definitely ($P < 0.01$)† less extreme than:	Least-squares estimate of the temporary effect of the event on the FEV (ml ± S.E.)	Temporary effect is definitely ($P < 0.01$)† less extreme than:
Chest illness with increased phlegm necessitating at least a week in bed in the previous 6 months	−13·2 ± 11·6	−40	2·6 ± 7·5	−15
Chest cold with the increased phlegm in the previous 6 months which did not necessitate a week in bed	1·0 ± 4·4	−9	−1·4 ± 2·9	−8
Chest episode with increased phlegm in the previous 6 months	−1·6 ± 4·3	−12	−1·3 ± 2·8	−8
Purulent sputum (mean purulence score of all bottles returned at one survey being 3 or more)	6·6 ± 8·6	−13	−6·6 ± 5·3	−19
H. Influenzae antibodies in the serum (only assayed in 1968)	−1·5 ± 11·1	−27	1·1 ± 10·3	−23

†One-sided 1 per cent confidence interval goes to mean − 2·33 S.E.s. The units are millilitres of FEV.

S.E.s, they enable us to set definite limits to the possible effects of the various events on the FEV.

None of the least-squares estimates of the permanent effects of chest colds, chest illnesses, *H. Influenzae*, or purulent sputum differed significantly from zero (in independent agreement with the lack of a significant correlation of any of these indices with FEV slope given FEV/H^3, smoking habits, and age). The mean permanent effects of these various events were definitely ($P < 0{\cdot}01$) very small. The conclusion that no permanent or temporary losses of FEV followed these various infective events is illustrated in Table 5.10 by the fact that the mean FEV residuals showed no significant pattern associated with their occurrence. We cannot, of course, say that no substantial FEV loss ever occurs as a result of a severe chest illness, but we can say that the chest episodes in our study, whether relatively severe or mild, did not, on the whole, cause such damage. Since chest episodes were more frequently reported by men with low FEV, they are the sort of illnesses that might be suspected of causing loss of FEV, but our findings provide no reason to justify this suspicion.

Our estimate of the mean permanent effect on the FEV of a chest illness serious enough to keep a man in bed for at least a week is a loss of only 13 ml (with standard error 12 ml, and thus compatible with no effect), and the true mean effect is definitely ($P < 0{\cdot}01$) less than a loss of 40 ml per illness. Since the mean frequency of such illnesses during our study was less than 1 in 20 man-years at risk, chest illnesses such as these cannot be an important cause of airflow obstruction in the general population.

Similarly, the true mean effect of the chest colds with increased phlegm which involved less than a week in bed or off work was definitely ($P < 0{\cdot}01$) less than 9 ml loss in FEV per chest cold. The mean loss in FEV caused by one such chest cold per winter for 20 years would thus be about zero, and definitely less than 200 ml. The mean frequency during our study was 0·35 chest colds per man per winter, so that it is not plausible to suppose that recurrent chest colds can be a significant cause of permanent airflow obstruction in the general population. This conclusion is supported by the independent evidence provided by the null correlations in the second column of Table 5.8, and by the discussion on pp. 108 and 133.

Lack of even a temporary effect on FEV after recovery from an infection. An alternative, though less important, aspect of the effect of chest episodes on FEV would be that they might cause a temporary reduction of FEV. This was found to be the case in a special

survey of all chest colds reported in the winter of 1962–3 among these men (Angel *et al.* 1965). A least-squares model which takes into account recovery from infection was estimated along similar lines to the test of the permanent effect of a chest episode Appendixes, section B.12). Although a temporary FEV reduction is found immediately after such chest episodes, the least-squares model shows that there is no appreciable effect about three months later. (Information about chest episodes was collected at six-monthly intervals.) Any FEV reduction must therefore be relatively transient and of little consequence. Using the same reasoning for temporary effects as for permanent effects, the mean temporary effect of a chest episode involving an increase in phlegm on the FEV about three months later is definitely ($P < 0{\cdot}01$) less than 8 ml (Table 5.11).

These studies of the immediate and long-term effects of our various indices of bronchial infection confirm independently the conclusion based on the multiple regression analysis that infective events such as we observed in our study do not cause any permanent loss of FEV and that the association of chest episodes with reduced FEV level either must be because low FEV causes chest episodes or must be due to a common association with some other factor. This other factor could well be mucus hypersecretion, since this is strongly correlated with FEV level and with chest episode frequency (see Chapter 6).

The effect of mucus hypersecretion on FEV

In discussing our findings on the relevance of mucus hypersecretion, it is important to remember that it was assessed only by measuring expectoration. It can reasonably be assumed that expectoration is correlated with the rate of production of mucus by the submucus glands in the large airways, but it would not necessarily be related to the average amount of mucus present in these airways. Nor is there any *a priori* reason for supposing that the amount of expectoration must be related to the amount of mucus produced by goblet cells in the small airways or present in these airways. Indeed, in status asthmaticus, in which mucus retention in the airways causes severe obstruction to airflow, expectoration is seldom marked and often absent. Nevertheless, it is widely considered that the reduction of FEV which has been found in subjects with expectoration, compared with those free from it, in many surveys is due to excess of mucus in the airways causing obstruction and we now present evidence that this is not the correct explanation.

All our indices of expectoration are strongly correlated with

Table 5.12. Multiple regression of FEV loss by expectoration

F-ratios (and regression coefficients) arising from the relationships between FEV level, FEV slope, and various measures of mucus expectoration. (See section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios.)

	FEV slope (ml/year) given age	FEV slope given age and FEV/H^3	FEV slope given age, FEV/H^3, and smoking	FEV/H^3 (cl/m^3) given age	FEV/H^3 given age and smoking habits
Sputum volume	13·3***	1·5	0·1	77·0***	60·0***
Mean sputum volume (ml) in bottles returned at surveys 1962–9	(−2·3)	(−0·8)	(−0·1)	(−2·1)	(−1·9)
Sputum probit	16·6***	2·8	0·2	77·4***	58·1***
As above, but subjected to a probit transformation before calculating the mean	(−6·0)	(−2·5)	(−0·6)	(−5·1)	(−4·5)
Phlegm score	19·8***	4·4*	0·2	76·2***	53·6***
Mean 0–4 scores assigned to replies to the phlegm questionnaire 1962–9	(−3·5)	(−1·7)	(−0·4)	(−2·7)	(−2·4)
MRC phlegm score	19·4***	5·4*	1·0	58·7***	41·6***
As above, but scored on the 0–2 basis recommended by the Medical Research Council (1966*a*)	(−7·9)	(−4·2)	(−1·8)	(−5·4)	(−4·7)
Initial sputum	3·7	0·0	0·5	38·0***	27·1***
Sputum volume (ml) at first (1961) survey	(−0·8)	(−0·05)	(0·3)	(−1·0)	(−0·8)

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$

FEV/H^3 given age (the last two columns of Table 5.12). Although this correlation is weakened somewhat by adjustment for smoking, it is not weakened very much, This shows that even in a group of men with identical smoking habits, there would still be a strong correlation between low FEV and indices of expectoration. Since smoking is a major cause of both abnormalities, the correlation would presumably be much weaker in non-smokers, but the existence of a strong correlation after allowing for current smoking habits shows that this correlation is not due just to both expectoration and low FEV being caused by smoking.

The quantitative relationship between mucus expectoration and low FEV/H^3 is given in Table 5.13. It is important to note that although the relationship between obstruction and expectoration is strong, nevertheless, among men with FEV/H^3 below 55 cl/m^3 (corresponding to FEV below 2·75 litres, in a man of height

Table 5.13. Expectoration by SFEV/H^3

Percentage distribution of mucus hypersecretion by age-standardized FEV/H^3 (SFEV/H^3: see Table 5.9) corrected for the original stratification. (The boundaries 55 cl/m^3 and 65 cl/m^3 divide our men into three large groups and, for a man aged 50, 171 cm tall, correspond to about 2·75 litres and 3·25 litres of FEV.)

	SFEV/H^3 < 55 cl/m^3	SFEV/H^3 55–65 cl/m^3	SFEV/H^3 < 65 cl/m^3	All SFEV/H^3
Mean 0–4 phlegm score				
0	25%	49%	46%	43%
0·01–0·99	18%	21%	31%	25%
1·00–1·99	16%	12%	13%	14%
2·00+	41%	17%	10%	19%
All phlegm questionnaire replies	100%	100%	100%	100%
Average score for all men in this SFEV/H^3 category	1·56 ± 0·13	0·77 ± 0·08	0·63 ± 0·06	0·88 ± 0·05
Mean sputum volume (ml)				
0	30%	51%	51%	46%
0·01–0·99	32%	32%	35%	33%
1·00+	38%	17%	14%	21%
All sputum volumes	100%	100%	100%	100%
Average volume for all men in this SFEV/H^3 category	1·41 ± 0·20 ml	0·62 ± 0·09 ml	0·46 ± 0·07 ml	0·72 ± 0·06 ml
Percentage of men in this SFEV/H^3 category	21·2	35·2	43·5	100·0

See Appendix G.2 on p. 256 for an age-standardized version of this table.

1·71 m), 30 per cent never managed, in some dozens of mornings spread over eight years, to produce any sputum. This was not merely due to lack of co-operation; it is confirmed by the fact that 25 per cent of the men with FEV/H^3 below 55 cl/m^3 never, in eight (or nearly eight) annual replies, claimed to have had any 'usual phlegm' for any part of the preceding winter. It follows that well over a quarter of this group of moderately obstructed men hardly ever consciously expectorated mucus. Table 5.13 also shows that many of the men with chronic mucus hypersecretion over an eight-year period had virtually normal FEV. Although the relationship between low FEV and indices of expectoration is thus not very precise (the correlation coefficient is 0·3), it is quite strong in that the regression coefficient (−1·9 or −2·1 ml/year) of FEV/H^3 on mean sputum volume corresponds to a difference in FEV of about 0·1 litres per ml of sputum expectorated in the first hour each morning. The difference in mean FEV between groups of

people whose measured sputum volumes differ by only a few millilitres might therefore be as much as half a litre. Thus, whatever is responsible for the correlation of low FEV with expectoration must be a major determinant of FEV itself, and it is important to understand it.

Is mucus hypersecretion a cause of permanent loss of FEV? Mucus hypersecretion is a factor which varies from time to time. If it caused more rapid FEV loss when it increased in severity, we should expect (as explained on pp. 71–3) to find a correlation between FEV slope and indices of expectoration *given* FEV/H^3 (so long as the variation were not so rapid as to be entirely smoothed out over an eight-year study). Table 5.12 shows that this is not the case, and that among men similar in FEV level, age, and smoking habits there is no tendency whatever for those with more expectoration to have steeper FEV slopes. This is a remarkably clear finding, and the null correlations in the central column of Table 5.12 deserve careful consideration. The data on which they are based are very extensive, and they completely exclude a number of hypotheses that might otherwise be entertained about the relevance of expectoration (or any processes which correlate with expectoration) to chronic airflow obstruction, such as: that variable hyper-reactive or allergic processes which cause mucus expectoration could also promote permanent loss of FEV; that asymptomatic infective processes which cause or correlate with mucus expectoration could permanently reduce FEV; or that hypersecretion by the mucus glands could actually promote infective processes which permanently reduce FEV or could itself be damaging to the airways.

Is temporary mucus hypersecretion a direct cause of temporary reduction of FEV? The findings in Table 5.12 would be consistent with the hypothesis that although neither mucus hypersecretion nor anything associated with it damages the airways, causing accelerated loss of FEV, the presence of excess secretion in the airways both obstructs airflow and causes expectoration. In this case, as mucus hypersecretion varied, FEV should also vary in the opposite direction. But this is not the case, for when indices of expectoration increased, there were quite definitely no average decreases of FEV of anything like 0·1 litres per ml of morning sputum. Table 5.14 illustrates this: for example, we can identify 194 sets of three successive survey attendances at which sputum was produced at the third but not at the first two (Table 5.14, top row). The increase in sputum volume must have been on average more than 1 ml, yet there is no evidence of a sudden loss of over 100 ml of FEV at the third survey.

Table 5.14. FEV residuals when expectoration was worse than usual

Mean FEV residuals (ml ± approximate S.E.) about individual FEV regression lines in relation to certain hypersecretory events. (Numbers of FEV residuals contributing to each mean in brackets.) The effects suggested by this table are formally estimated in Table 5.15.

Nature of event	Mean FEV residual at all surveys when the event was present	Mean FEV residuals at three consecutive surveys which were all attended with the relevant event only present at the last one		
		(a) Event absent (12 months before event)	(b) Event absent (6 months before event)	(c) Event present
A non-empty sputum bottle was returned	−1 ± 2 (3988)	−13 ± 11 (194) No sputum	28 ± 11 (194) No sputum	−5 ± 10 (194) No sputum
The mean volume in the sputum bottles returned is 2 ml or more	−1 ± 3 (1819)	5 ± 11 (155) <2 ml	15 ± 12 (155) <2 ml	0 ± 11 (155) ⩾2 ml
Usual phlegm is reported to have been produced last winter	2 ± 3 (2336)	−10 ± 6 (645) Phlegm not usual last winter	0 ± 6 (645) Not asked (winter survey)	−9 ± 6 (645) Usual phlegm last winter
Usual phlegm is reported to have been produced during 3 or more months last winter	0 ± 4 (1423)	−2 ± 8 (433) <3 months phlegm last winter	−12 ± 8 (433) Not asked (winter survey)	11 ± 8 (433) ⩾3 months phlegm last winter

Moreover, if we study men who sometimes produced empty sputum bottles and at other times did not, we find their FEV when they did produce some sputum differed little, if at all, from their FEV regression line (Table 5.14, column 1). The last two columns of Table 5.15 report a formal least-squares analysis (section B.12 of Appendixes) which confirms this null finding and gives confidence limits to the lack of any temporary effect on FEV of an increase in recorded expectoration. For each type of temporary increase in expectoration which is recorded, the associated temporary decrease in FEV is about zero and each upper 99 per cent confidence limit for the decrease is less than 0·01 litres. If the correlation between FEV and indices of expectoration was due to mucus hypersecretion directly causing reduction of FEV then, in view of its strength (0·1 litres per ml of sputum), there would be an appreciable FEV reduction when recorded expectoration increased, and this was not observed.

Our evidence is therefore inconsistent with mucus hypersecretion directly lowering FEV either temporarily or progressively and we therefore have to postulate that the correlation between these two abnormalities is due to their having a common cause. This common cause cannot be one which *varies* during adult life causing either temporary or progressive loss of FEV when it is more active, for the reasons given above, and we are therefore left with *persistent* common causes. These might be of two distinct types:

1. A common cause which is approximately constant throughout adult life. Although FEV level would tend to be lower in people who have it, this would be non-progressive, so that FEV slope would be normal. This cause could, for example, be some infective or environmental damage to the lungs in childhood which permanently reduced FEV and promoted continuing expectoration.
2. A common cause which is either constant throughout adult life or changes at an extremely steady rate. It would cause expectoration, and an increased rate of permanent loss of FEV (steeper FEV slope). For example, in smokers, susceptibility to development of expectoration and susceptibility to development of airflow obstruction might both have at least one genetically determined biochemical aspect, such as excess macrophage trypsin or antitrypsin activity, in common. Less plausibly, FEV-reducing lesions, which progress steadily throughout life, might promote expectoration.

If the whole truth lay in alternative (1), no correlation should exist between expectoration and FEV slope. But Table 5.12 shows

Table 5.15. FEV changes when expectoration was worse than usual

Limits imposed by our data on the biggest possible effects (permanent or temporary) of various hypersecretory events on the FEV (in ml). Least-squares estimates based on the differences within particular men of the FEV changes when various events occur from the FEV changes at other times.

	Least-squares estimate of the permanent effect of the event on the FEV	The permanent effect is definitely ($P < 0{\cdot}01$)† less	Least-squares estimate of the temporary effect of the event on the FEV	Temporary effect is definitely ($P < 0{\cdot}01$)†
A non-empty sputum bottle was returned	$-5{\cdot}4 \pm 4{\cdot}0$	-15	$-2{\cdot}6 \pm 2{\cdot}8$	-9
The mean volume in the sputum bottles returned is 2 ml or more	$-2{\cdot}4 \pm 5{\cdot}6$	-15	$-0{\cdot}1 \pm 3{\cdot}4$	-8
Usual phlegm is reported to have been produced last winter	$3{\cdot}4 \pm 5{\cdot}4$	-9	$-0{\cdot}6 \pm 1{\cdot}4$	-4
Usual phlegm is reported to have been produced during 3 or more months last winter	$1{\cdot}4 \pm 6{\cdot}8$	-14	$-0{\cdot}4 \pm 1{\cdot}9$	-5

†One-sided 1 per cent confidence interval goes to mean − 2·33 S.E.s. The units are millilitres of FEV.

that there is in fact a highly ($P < 0{\cdot}001$) significant relationship between them. We are therefore left, finally, with alternative (2) and conclude that there must be some common cause of expectoration and steep FEV slope which either remains constant throughout adult life in each individual or changes very steadily during adult life but does not *vary* erratically from time to time.

Since the common cause affects FEV slope so strongly, it is not possible to say for certain whether it also affects FEV level. However, it is of interest to note, in Table 5.12, that if the observed correlations in column 1 (between FEV slope and expectoration) had operated for 35–45 years, which is reasonable if the correlation is due to the lifelong operation of a constant common cause, then the regression coefficients in column 4 (of FEV/H^3 on expectoration) would have resulted. This shows that there is no need to postulate any extra mechanism beyond the established correlation between more rapid FEV loss and expectoration to explain the correlation between FEV/H^3 and expectoration.

Our data can thus be wholly accounted for by a common cause which is constant throughout life and which predisposes to expectoration and to more rapid FEV loss in those individuals who suffer it most strongly. The data exclude the possibility that the common cause varies appreciably within individuals (and thus exclude the possibility that mucus hypersecretion, which does vary, or any of its close correlates, could promote permanent obstructive changes), but do not exclude the possibility that the common cause progresses steadily within certain individuals. Thus, our data do not exclude the possibility that obstructive changes, which do develop steadily, could themselves promote mucus expectoration. However, since we can think of no plausible mechanism whereby this could occur, we prefer to suppose that the only connection between the two abnormalities is that susceptibility to one condition is partially linked to susceptibility to the other.

Allergies

None of the positive answers to questions concerning a personal or family history of hay fever at the initial survey (Appendixes, section A.3) nor of those to a more detailed questionnaire on allergic manifestations in the 1966–7 surveys (section A.6) were correlated significantly with FEV slope. (However, the 17 men who were *clinically* asthmatic did on average have steeper slopes than other men—see below.) A positive answer to the question about migraine did correlate with slope (F-ratio = 4·8, $P < 0{\cdot}05$; Table 5.16) after adjustment for FEV/H^3, age, and smoking habits, but this is almost

Table 5.16. Multiple regression of FEV loss by hyperreactivity

F-ratios (and regression coefficients) arising from the relationships between FEV level, FEV slope, and various indices suggestive of hyperreactivity. (See section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios.)

	FEV slope (ml/year) given age	FEV slope (ml/year) given age, FEV/H^3 and smoking habits	FEV/H^3 (cl/m^3) given age and smoking habits
Asthma	8·9**	6·8**	12·9***
Clinical asthmatic: see Appendixes section E.2 (0 = never, 1 = yes; 2 per cent were thus 'asthmatic').	(−22)	(−18)	(−11)
Eosinophilia	3·7	4·2*	3·9*
Were eosinophils (grade 3 or 4) found at any of the surveys 2, 7 or 9 in the sputum (0 = never, 1 = yes), given mean sputum volume 1962–9?	(−7)	(−7)	(−3)
Migraine	2·4	4·8*	0·2
History of migraine reported in 1967?† (0 = no, 1 = yes, 0·14 = not present in 1967. N.B. proportion with migraine = 0·14)	(−5)	(−7)	(+1)

†None of the other questions asked in 1967 about allergic conditions (hay fever, eczema, or urticaria in self or in first degree relatives) was negatively correlated with FEV/H^3 or with FEV slope.

*$P < 0{\cdot}05$; **$P < 0{\cdot}01$; ***$P < 0{\cdot}001$.

certainly a statistical fluke since no correlation between migraine and FEV/H^3 exists. We conclude that allergy, as assessed by our questions about the presence or absence of various allergic diseases other than asthma, is irrelevant to the development of airways obstruction in the general population.

A more objective index of bronchial allergy is sputum eosinophilia, which was assessed in the sputum specimens returned at surveys 2, 7, and 9. We have divided the men into two groups according to whether they did (1) or did not (0) have sputum with a mean eosinophilia grade of 3 or 4 (see p. 32) at one of these three surveys. This index is necessarily zero for men who produced no sputum at these surveys and so is correlated with mucus hypersecretion as well as with allergy. Despite the crudeness of this index of eosinophilia, after adjustment for age and mean sputum

volume it was still associated with a slightly (3 cl/m³) lower FEV/H^3 and a slightly (7 ml/year) steeper FEV slope (Table 5.16). These correlations are not accounted for by a correlation with asthma, but they are weak and could ($P = 0{\cdot}05$) be due to chance.

The mean FEV slope of the 17 asthmatic subjects in the Follow-Up Group was significantly steeper (22 ± 7 ml/year steeper) than the average for all men, and this correlation between asthma and FEV slope persisted after adjustment for FEV level and smoking (Table 5.16). (Three other, presumably more severe, asthmatics were excluded because they were on regular bronchodilators or steroids—see section B.4 of the Appendixes.) The asthma in most of these 17 men was mild, only 3 having mean FEV levels below 2 litres. Rather surprisingly, the variation of their FEV readings about their FEV regression lines was no greater than that of the non-asthmatics. Ten of them were cigarette smokers (mostly irregular, but mean consumption 14 cigarettes/day), 5 were ex-smokers, and only 2 had never smoked.

The fact that their FEV slope was as steep as the mean FEV slope for the heavier non-asthmatic cigarette smokers indicates that even such 'mild' asthmatics may be more liable to develop progressive airflow obstruction than non-asthmatics. If this is the case, then perhaps very slight degrees of asthma, not sufficient to merit clinical diagnosis, may also be relevant to the development of chronic airflow obstruction. Although we did assess responsiveness to histamine and to isoprenaline in a few of our obstructed men, finding no evidence of abnormality, our study did not include any reliable quantitative assessment of the asthmatic tendency of each man and we cannot, therefore, assess the relevance of asthma to the aetiology of obstructive airways disease. However, clinical asthma was certainly not a common feature among the obstructed men.

Other factors

Change of airways resistance on smoking a cigarette. The only direct index we have of bronchial hyperreactivity was the change of airways resistance on smoking a cigarette. This was not correlated with FEV slope. Van der Lende *et al.* (1973) have shown that hyperreactivity, as assessed by histamine threshold measurements, is correlated with FEV%VC, but the correlation is not strong and may perhaps be largely accounted for by a common correlation of both with expectoration. As an index of 'variability of airflow obstruction', we also correlated the standard deviation of FEV readings about each individual's regression lines, the average scatter (maximum–mean) of FEV readings at each survey, and the difference between average

Table 5.17. Multiple regression of FEV loss by remaining factors

F-ratios (and regression coefficients) arising from the relationships between FEV level or FEV slope and physical characteristics, childhood illness questionnaires or X-ray findings. (See section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios.) 1967 absentees (A) are assigned the average value or score among 1967 attenders.

	FEV slope (ml/year) given age	FEV slope (ml/year) given age, FEV/H^3, and smoking habits	FEV/H^3 (cl/m³) given age and smoking habits
1–3 relate to the 1967 questionnaire on childhood illnesses (A denotes absent in 1967)			
1. *Childhood bronchitis* Did you suffer from bronchitis before age 15? (0 = no, 1 = yes, 0·07 = A)	0·0 (0)	0·8 (+4)	10·2** (−6)
2. *Childhood pneumonia or pleurisy* Did you suffer from pneumonia or pleurisy before age 15? (0 = no, 1 = yes, 0·11 = A)	0·7 (−3	0·0 (0)	3·9* (−3)
3. *Other childhood illnesses* Largest F-ratio for a correlation with any other of 7 illnesses before age 15	2·6	2·4	2·0
Emphysema Did the chest X-ray in 1967 indicate emphysema? (0 = no, 1 = localized, 2 = generalized, 0·10 = A)	23·5*** (−16	9·1** (−10)	24·5*** (−6·7)
Standing height (cm) in 1961	5·6* (−0·4	1·5 (−0·2)	†
Weight (kg) in 1961	2·5 (0·2)	0·9 (0·1)	5·8 (−0·1)
Skinfold thickness on the hand (mm) in 1967 (2·6 = A)	1·5 (3)	0·3 (1)	0·0 (0)

†FEV/H^3 is strongly related to height, because its denominator is the cube of height: see section B.6 of the Appendixes.
*$P < 0{\cdot}05$; **$P < 0{\cdot}01$; ***$P < 0{\cdot}001$.

winter and summer FEV levels with FEV slope. None of these correlations with FEV slope approached significance.

Childhood illnesses. We originally asked questions about childhood illnesses in the hope that any constitutional liability to develop disabling respiratory impairment might be indicated by a higher frequency of childhood illnesses (Appendixes, section A.7). None of the childhood illnesses which we enquired about were correlated

significantly with FEV slope. Only a 'childhood history' of bronchitis (given by 7 per cent of men) correlated with FEV level (Table 5.17), and the correlation is so weak that we are inclined to attribute it to reporting bias, whereby obstructed men more readily recall past illnesses. Even if it is due to persistent lung damage in some men, the lack of a correlation with FEV slope suggests that a history of 'childhood bronchitis' given by a middle-aged man does not indicate a constitutional liability to subsequent progressive airflow obstruction.

Height, weight, and skinfold thickness. There was no association between height and the slope of log FEV, which indicates that height is only a 'scale factor' and that tall men do *not* have more fragile lungs than short men. This conclusion has been disputed, and is discussed in more detail in section B.13 of the Appendixes. There was a weak correlation between weight and FEV slope, the heavier men having less steep slopes than the lighter men. This correlation persisted after adjustment for FEV level and age but disappeared after adjustment for smoking habits and can be attributed to the fact that non-smokers and ex-smokers were heavier (mean 76 kg, after correction for the 1961 stratification) than smokers (mean 71 kg).

Skinfold thickness on the back of the hand was not correlated with FEV/H^3 given age and smoking habits, nor with FEV slope given age (Table 5.17). It is inversely correlated with weight and thus with smoking, and thus (weakly) with FEV/H^3 given age, but this correlation vanishes after adjustment for smoking.

Radiological emphysema. Although only 10 per cent of our men were classified as having evidence of emphysema on their chest X-rays, this abnormality was strongly correlated with low FEV/H^3 and steep FEV slope (Table 5.17). The latter correlation is reduced, but still persists, after adjustment for FEV/H^3, smoking habits, and age.

By old age, some smokers have extensive emphysema while other men with similar smoking habits may have very little emphysema. Extensive emphysematous changes reduce FEV considerably. If these changes develop gradually over decades, then the average lifelong rates of their development must be markedly different in different men, even if their smoking habits are the same. These average lifelong rates of development of emphysema will, in middle age, correlate with the rates of loss of FEV and with the amounts of emphysema already present. This will cause the (observed) correlation between FEV slope and radiological emphysema, given

smoking, and, because FEV level is an imperfect measure of emphysema, adjustment for FEV/H^3 and age will not extinguish this correlation.

Therefore, it is not necessary to postulate that the presence of emphysema somehow accelerates FEV loss in order to account for the observed correlations between emphysema and FEV slope. Such correlations would be expected to arise anyway, merely as a 'horse-racing' effect (p. 71).

6 Factors affecting bronchial infection, mucus hypersecretion, and changes in cigarette consumption

Summary

CHEST EPISODES are strongly correlated with indices of expectoration, less strongly with indices of airflow obstruction, and weakly with smoking. After adjustment for phlegm score, only a weak correlation with airflow obstruction remains. Since expectoration and low FEV have a common cause, this suggests that chronic mucus hypersecretion increases rather than decreases liability to chest episodes. This suggestion is weakly confirmed by our finding no tendency for expectoration to be increased, except temporarily, after a chest episode, and by the lack of any significant tendency for expectoration to become greater in the course of the study in men who have more frequent episodes.

H. influenzae antibodies are independently related to smoking, expectoration, and sputum purulence but not to FEV level or slope or chest episodes. This suggests that chest episodes represent a different type of infection from those causing antibodies and purulence, although correlations with purulence are obscured by its inevitable link with expectoration.

Apart from their correlation with airflow obstruction and chest episodes, indices of expectoration are highly correlated with smoking, and expectoration declined in men who reduced their smoking. Men who had symptoms tended to reduce their smoking more than those who had not.

Introduction

Severe airflow obstruction develops gradually and largely irreversibly over many years and is necessarily disabling, whether or not mucus hypersecretion accompanies it; mucus hypersecretion alone is not disabling. Although we have found evidence that neither mucus hypersecretion nor the bronchial infections we recorded play any causal role in the accelerated development of airflow obstruction, the

Table 6.1. Multiple regression of chest episode frequency

F-ratios for correlations of various factors with percentage chest episode frequency from 1962 to 1969 (regression coefficients in brackets). (See Appendixes, section B.15 for computational details and p. 74 for an explanation of F-ratios.)

Factor	F-ratios given age† only	F-ratios given age and mean phlegm score	F-ratios given age, phlegm, and FEV/H^3
Mean phlegm score 1962–9 (scored 0–4 from questionnaires)	231·0*** (8·4)	—	—
Mean sputum probit 1962–9 (from sputum volumes)	122·7*** (12·0)	0·5 (N.S.)†	0·1 (N.S.)
Mean sputum volume (ml)	65·1** (3·8)	0·3 (N.S.)	1·2 (N.S.)
FEV/H^3 (cl/m^3)	46·3** (−0·47)	9·5** (−0·20)	—
FEV (litres)	40·6** (−8·4)	5·5* (−2·9)	0·0 (N.S.)
FEV%VC	30·6** (−0·48)	5·3* (−0·18)	0·1 (N.S.)
VC (litres)	15·8** (−4·6)	1·8 (−1·4)	0·0 (N.S.)
X-ray emphysema (0, 1, or 2 if measured, 0·10 otherwise)	12·1** (9)	3·1 (4)	1·7 (N.S.)
Smoking (3 groups: zero, light, heavy)	10·7÷2 * (heavy +5%, light +5%)	3·2÷2 (N.S.)	3·8÷2 (N.S.)
Present hay fever	9·5** (7)	5·5* (5)	5·3 (5)
Childhood bronchitis††	5·9* (9)	2·3 (N.S.)	1·5 (N.S.)
Clinical asthma	4·8* (13)	5·5* (12)	3·9 (10)
Sputum purulence frequency 1962–9 given mean sputum volume and probit	1·2 (N.S.)	4·8* (−18)	6·6* (−21)
Present migraine	4·1* (5)	5·7* (6)	6·1* (6)
H. influenzae antibodies	4·0* (4)	0·3 (N.S.)	0·2 (N.S.)

There were no significant correlations between chest episode frequency and any of the following factors: age, height, weight, variability of FEV readings, sputum probit regression, skinfold thickness, other allergic conditions nor, among smokers, with cigarette regression or frequency of use of filtered cigarettes.

† Although no significant correlation between chest episode frequency and age existed, many of the other factors are correlated with age, and regressions given age are therefore slightly more relevant than direct regressions.

Non-significant F-ratios are marked N.S.; significant ones are asterisked.

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

†† The few men claiming childhood catarrh also had more chest episodes.

causal relationships of hypersecretion and infections with each other and with other factors that we have measured in our study are of some interest in relation to the natural history of chronic non-specific lung disease. They may also suggest ways of preventing what may be troublesome and temporarily disabling conditions.

Factors correlated with bronchial infection

Factors affecting chest episode frequency

Chest episode frequency is strongly correlated with indices of mucus hypersecretion, with indices of airflow obstruction (most significantly with FEV/H^3), with X-ray emphysema, and with smoking habits (Table 6.1). There are also less strong but still significant relationships with migraine and indices of current allergy (hay fever and clinical asthma) and with a history of childhood bronchitis. There is a weak relationship with the presence of *H. influenzae* antibodies.

After adjustment for phlegm score and age, no strong correlations remain. There are still small but significant relationships with indices of airflow obstruction, hay fever, migraine, and childhood bronchitis. The relationships with smoking and with *H. influenzae* antibodies disappear.

The strong correlations of chest episode frequency with all indices of expectoration indicate that it must be closely correlated with the true average rate of mucus hypersecretion during our study, of which these indices are certainly imperfect measurements. The F-ratios for the correlations of chest episode frequency with each measure of obstruction (FEV/H^3, FEV, FEV%VC, VC, or X-ray emphysema) are all highly significant ($P < 0.001$) before adjustment for phlegm score, but they are all reduced by at least 75 per cent after adjusting for phlegm score (Table 6.1). This is the qualitative pattern we would expect to find (Appendixes, section B.14) if chest episode frequency and airflow obstruction were separately and independently correlated with real mucus hypersecretion but not with each other, given real mucus hypersecretion.

Table 6.2 demonstrates that, given mucus hypersecretion, there is no correlation between airflow obstruction and chest episode frequency in the least obstructed 90 per cent of men. Within phlegm score groups there is a slightly higher chest episode frequency in only the most obstructed 10 per cent of our sample. Because of the imperfections of phlegm score, the effect on chest episode frequency of having a low FEV/H^3 (below 45 cl/m^3) given *real* mucus hypersecretion must be less than is suggested by inspection of the rows of Table 6.2 (Appendixes, section B.14). It must, therefore, be small

Table 6.2. Chest episode frequency by mean phlegm score and FEV/H^3

This table estimates what would have been observed if the 1961 sample had not been stratified. Numbers of men in each cell are given in brackets as percentages of the unstratified Follow-Up Group. Approximate† S.E.s are indicated.

Mean phlegm score 1962–9	FEV/H^3 (cl/m^3) <45	45–55	55–65	>65	All men	Average sputum volume (ml) of all men in this phlegm score range
0	9·6 ±6·6 (2·1%)	10·2 ±3·9 (5·5%)	9·4 ±2·6 (12·8%)	8·7 ±2·0 (22·1%)	9·1 ±1·4 (42·6%)	0·1
0·1–1·0	27·7 ±7·3 (1·3%)	16·8 ±4·2 (4·7%)	17·9 ±3·1 (9·2%)	18·0 ±2·6 (12·5%)	18·2 ±1·7 (27·7%)	0·3
1·1–2·0	32·5 ±6·6 (1·2%)	23·6 ±4·8 (3·2%)	28·7 ±4·2 (4·2%)	27·0 ±4·3 (3·7%)	27·2 ±2·4 (12·2%)	1·1
>2	39·7 ±3·5 (4·4%)	37·3 ±4·0 (3·6%)	37·5 ±3·4 (5·4%)	32·3 ±3·6 (4·2%)	36·8 ±1·8 (17·5%)	2·6
All men	30·0 ±2·7 (8·9%)	20·3 ±2·1 (17·0%)	19·2 ±1·6 (31·6%)	15·3 ±1·4 (42·5%)	18·7 ±0·9 (100%)	0·7

† These S.E.s were calculated as in Appendixes, section B.7. If, here or in Table 6.3, allowance had been made for the dependence of the S.D. on the mean chest episode frequency, only the S.E.s in the first line of this table (or Table 6.3) would have been substantially changed, being reduced by about a third.

and could well be zero, especially since a reporting bias exists; minor illnesses will tend to be more troublesome and thus more likely to be reported in men with the most severe degrees of airflow obstruction.

The correlation between sputum purulence and chest episode frequency, *given sputum volume and probit* (see p. 27), is significant but negative; the greater the purulence, the fewer episodes. If sputum volume is increased when it is purulent, adjustment for volume at the time of purulence would be an over-adjustment for persistent mucus hypersecretion and would cause a negative bias in the correlation between sputum purulence and chest episode frequency (Appendixes, section B.14). The finding is thus also consistent with there being a null or a positive correlation between purulence of sputum at the time of each survey and the frequency of chest episodes between surveys, and we are therefore completely unable to characterize the true relationship between mean purulence and mean chest episode frequency.

The dependence of chest episode frequency on phlegm score and on FEV/H^3 or smoking habits is shown in Tables 6.2 and 6.3. Table 6.3 conflicts with a previous report of a positive effect of smoking on chest illnesses in men who returned empty sputum bottles on the single occasion they were seen (Fletcher 1965). This discrepancy is probably because our present mean phlegm score, although still imperfect, is a more accurate index of mucus hypersecretion than is a single sputum volume measurement. This illustrates how misleading it may be if causality is studied by multiple regression unless the 'given' quantities in the regression have been very accurately measured. The fact that the correlation with phlegm score is closer than that with sputum probit, and this in turn is closer than that with sputum volume, suggests that this is the order of accuracy with which these indices represent the men's true average level of mucus hypersecretion (Fletcher *et al.* 1974). Part of the association of chest illnesses with phlegm score could be spurious, however, for both chest illness frequency and phlegm score are based on positive answers to questions and some men probably have a tendency to answer 'Yes' or 'No' to any question about symptoms. A genuinely strong correlation between mucus hypersecretion and illness frequency is also indicated by the high correlations of chest episode frequency with sputum volume or probit.

Does chronic hypersecretion cause chest episodes?

We now have to consider whether the relationship between mucus hypersecretion and chest episodes is causal and, if so, which causes which: either might theoretically encourage the other. On the one

Table 6.3. Chest episode frequency by mean phlegm score and smoking habits

This table estimates what would have been observed if the 1961 sample had not been stratified. Numbers of men in each cell are given in brackets as percentages. Approximate S.E.s (see footnote to Table 6.2) are indicated.

Mean phlegm score 1962–9	Non-smokers	Ex-smokers, stopped before 1961	Men who smoked at some summer surveys, by mean of the cigarette consumptions reported at summer surveys (cigarettes/day)				All men	Average sputum volume (ml) of all men in this phlegm score range (ml)
			0–5	>5	>15	>25		
0	9·5 ±2·5 [illegible]	10·7 ±3·2 [illegible]	7·7 ±3·3 [illegible]	8·5 ±2·7 [illegible]	10·4 ±4·6 [illegible]	4·5 ±13·8 [illegible]	9·1 ±1·4 [illegible]	0·1
0·1–1·0	23·9 ±4·8 (1·9%)	21·5 ±4·5 (4·2%)	18·6 ±4·0 (5·5%)	19·4 ±2·9 (10·2%)	13·1 ±4·7 (3·8%)	9·4 ±6·7 (2·1%)	18·2 ±1·7 (27·7%)	0·3
1·1–2·0	25·6 ±9·8 (0·5%)	36·8 ±6·4 (1·4%)	23·0 ±5·1 (2·7%)	27·2 ±4·0 (3·9%)	30·7 ±5·2 (3·0%)	13·2 ±11·2 (0·8%)	27·2 ±2·4 (12·2%)	1·1
>2	41·5 ±9·6 (0·3%)	42·1 ±8·8 (0·6%)	30·3 ±4·4 (2·9%)	38·1 ±2·8 (6·7%)	37·9 ±3·5 (5·2%)	36·9 ±5·6 (1·9%)	36·8 ±1·8 (17·3%)	2·6
All men	13·9 ±2·1 (10·3%)	17·5 ±2·1 (14·4%)	16·3 ±2·1 (19·4%)	19·6 ±1·5 (34·4%)	23·3 ±2·2 (16·4%)	20·0 ±4·0 (5·1%)	18·7 ±0·9 (100%)	0·7

hand, excessive mucus production, by blocking airways and inhibiting normal bronchial drainage, could encourage the growth of infective agents; on the other, the acute increase of mucus secretion which occurs with clinical infections might tend to become persistent, after repeated episodes, as a reaction to a persistent low level of inflammation. We have already concluded (p. 100) that the association between airflow obstruction and mucus hypersecretion exists because they are caused by linked susceptibilities. We also find that there is a correlation between chest episode frequency and airflow obstruction which is largely extinguished by adjustment for phlegm score, while the correlation between phlegm score and airflow obstruction is not extinguished by adjustment for chest episode frequency. This shows that chronic mucus hypersecretion is a major cause of chest episodes. (The same argument applies if we consider smoking habits rather than airflow obstruction.) This argument does not exclude the opposite possibility, that repeated chest episodes might also cause some chronic mucus hypersecretion; indeed, since chest episodes do by definition cause some temporary hypersecretion it would be surprising if this were not so. However, the relative magnitudes of the correlations between airflow obstruction, mucus hypersecretion, and chest episode frequency suggest that this effect cannot be very marked.

Do chest episodes cause any chronic hypersecretion?

We have two further ways of clarifying this interrelationship. The first is to look at short-term changes in sputum volume after chest episodes, by taking triplets of successive surveys at the middle one of which a man reported a chest episode but at the first and third of which he did not (Fig. 6.1). We can then see whether, at a mean

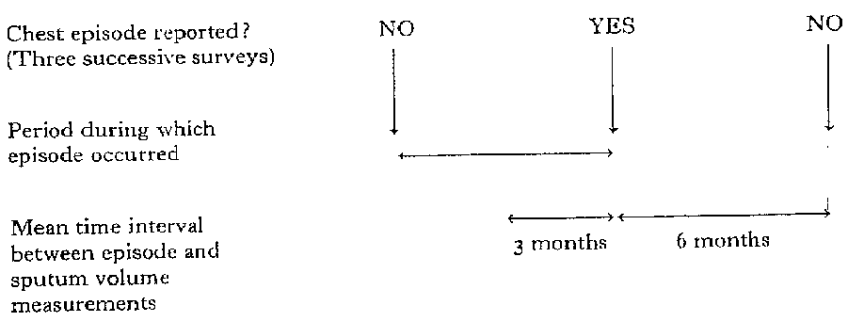


Fig. 6.1. Basis of analysis in Table 6.4

The successive surveys at which a chest episode is, and then is not, reported are on average about 3 and 9 months after the episode.

Table 6.4. Changes in expectoration when infective events occur

Sputum volume before and after 603 isolated chest episodes 1962–9 where all three relevant surveys were attended

Survey	Mean sputum volume† (ml)
(a) One before episode reported (no episode)	0·84 ± 0·07
(b) One at which episode reported	1·10 ± 0·08
(c) One after episode reported (no episode)	0·82 ± 0·07
(c)–(a)	−0·02 ± 0·05
(d) One before illness reported (no illness)	1·46 ± 0·24
(e) One at which illness (+ week in bed) reported	1·78 ± 0·23
(f) One after illness reported (no illness)	1·38 ± 0·23
(f)–(d)	−0·08 ± 0·21

† Zero if no bottle returned.

period of some nine months after the episode, there was any measurable increase in mucus hypersecretion compared with that observed on average three months before the episode. The sputum volume at the second of the three surveys indicates whether there was an increase in volume on average three months after the episode. This analysis shows (Table 6.4) that there was, as would be expected since chest episodes by definition involve a temporary increase in phlegm, more sputum produced at the survey at which the chest episode was reported, but there was no evidence of any increase of sputum volume at the next survey, six months later. This was true both for chest episodes as a whole and for the more serious type of episode, chest illnesses, which involve a week in hospital or in bed.

The second approach is to look at longer-term changes in the two parameters. We examined the relationship between chest illness frequency and sputum slope, arguing that, if chest episodes caused a permanent increase in mucus hypersecretion, men with more frequent chest episodes should show a steady rise in mucus hypersecretion compared with those who had fewer chest illnesses. We found no significant correlation, but this may be due simply to the imprecision of sputum slope as a measure of changes in mucus hypersecretion. A study of changes in phlegm score (Table 6.5) showed no clear evidence that chest episodes caused any permanent increase in mucus hypersecretion, but these results are confused both by random variation and by the secular changes in mucus hypersecretion which appear to have affected all the men in our study (see Chapter 4).

The methods described on pp. 87–9 to study the maximal possible permanent effect of infective agents on FEV can also be used to study the maximal possible permanent increase of sputum conse-

Table 6.5. Phlegm score changes by chest episode frequency

Effect of chest episode frequency on phlegm score among those who attended 1–3 summer surveys from 1962 to 1964 and 1–3 summer surveys from 1967 to 1969 (numbers of men in brackets).

Chest episode frequency 1964–8	Mean percentage chest episode frequency 1964–8	Mean phlegm score 1962–4	Mean phlegm score 1967–9	Change in phlegm score 1962–4/1967–9
Less than 20 per cent (404 men)	4·5 ±0·3	0·84 ±0·06	0·61 ±0·06	−0·23 ±0·04
20 per cent or more (355 men)	44·8 ±1·0	1·81 ±0·08	1·65 ±0·08	−0·16 ±0·05

quent on either a chest illness or a chest episode. We find by such a study that the least-squares estimates of the permanent effect of a chest episode or chest illness on the sputum volume are both, in fact, negative! (although not statistically significantly so). The estimated effect of a chest episode is to *decrease* all subsequent sputum volumes by 0·008 ±0·032 ml, which implies that the permanent effect of a chest episode increasing the subsequent sputum volume is definitely ($P < 0·01$) less than +0·067 ml. The estimated effect of a chest illness involving a week in bed is to *decrease* all subsequent sputum volumes by 0·167 ±0·101 ml, which implies that the permanent effect of a chest illness increasing the subsequent sputum volumes is definitely ($P < 0·01$) less than +0·068 ml. These studies are not as unequivocal as the studies of the permanent effects of chest episodes and illnesses on the FEV, but as far as they go they do confirm that chest episodes and chest illnesses have no *permanent* effect on subsequent mucus hypersecretion.

We conclude that the relationship between phlegm score and chest illness frequency is partly due to chest episodes causing a temporary increase in phlegm, but predominantly due to chronic mucus hypersecretion causing increased liability to chest episodes. After allowing properly for this effect, men with reduced FEV (i.e. with some degree of airflow obstruction) may be no more likely to suffer chest episodes than those with more normal levels but the same degree of mucus hypersecretion. There is also a slight indication that men who report migraine or allergic diseases (particularly asthma or hay fever) and those who give a history of bronchitis in childhood may have an increased liability to report chest episodes, although since all are assessed by questionnaire, reporting biases will affect all of them similarly and no real association may exist.

Haemophilus influenzae antibodies

We have already published our finding (May *et al.* 1973) that the only factors significantly and independently related to the occurrence of serum antibodies to *H. influenzae* are smoking, phlegm production, and sputum purulence. The lack of any relationship of chest episode frequency with *H. influenzae* antibodies after adjustment for phlegm score is surprising, whether or not May *et al.* are correct in postulating that detectable *H. influenzae* antibodies may not persist for long after active infection with *H. influenzae* has ended. These two indices must represent completely different aspects or types of bronchial infection, for their correlates are so dissimilar; the occurrence of *H. influenzae* antibodies is strongly correlated with smoking habits and, mainly through smoking, with phlegm score, whereas chest episodes are strongly correlated with phlegm score and, only through phlegm score, with smoking.

Factors affecting sputum purulence

The multiple regression analysis of the mean frequency of production of purulent sputum is complicated by the unavoidable correlation between sputum volume and sputum purulence, because without some volume of sputum, purulence is necessarily zero.† This means not only that we cannot interpret this particular correlation, which is very strong (the F-ratio for the correlation between sputum purulence frequency and sputum probit is 281·0) but also that all correlates of sputum volume are also correlated with sputum purulence. Therefore we can study only correlations with purulence given volume and probit.

The results of this analysis are given in Table 6.6, but because all the correlations are regressions given mucus hypersecretion, they are virtually uninterpretable. Although the correlation with $\log(FEV/H^3)$ is positive (correlations with our other standard indices of airways obstruction are also significant at the 1 per cent level, but with smaller F-ratios), we do not know whether a genuine association between obstruction and purulence in the bronchi exists in our population. Despite the correlation with chest episode frequency being zero, we know that about a third of chest episodes cause the sputum to become purulent at the time of the episode (Angel *et al.* 1965), so some correlation between the two should exist (p. 110).

Purulence was an uncommon finding, seen at less than 5 per cent

† Unfortunately, the individual survey measures of sputum volume and sputum purulence were means of up to three specimens. Had we recorded separately the volume and purulence of the sputum in each individual bottle, we could have looked at the correlations of volume with purulence excluding all empty bottles, but we are now unable to do this.

Table 6.6. Multiple regression of sputum purulence

F-ratios for the correlations of various factors with sputum purulence given sputum volume and probit (see section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios).

Factor	F-ratio	Comment
Smoking (3 groups)	0·1 ÷ 2	No effect whatever
Smoking (9 groups)	3·6 ÷ 8	No effect whatever
Chest episode frequency 1962–9	1·2	Weak negative correlation: see p. 110
log(FEV/H^3)	11·9***	Men with low FEV are more likely to have purulent sputum, $P < 0.001$
H. influenzae antibodies	10·0**	Positive correlation, $P < 0.002$
H. influenzae antibodies given log(FEV/H^3)	8·8**	$P < 0.01$

**$P < 0.01$; ***$P < 0.001$.

of the survey attendances from 1962 to 1969, and some of the pus recorded may have originated from the para-nasal sinuses. Thus, any real relationships with purulent sputum originating from the bronchi are obscured, and we can only conclude that our study has provided no useful information about the aetiology or role of purulence, other than that it is not, nor is it correlated with, a cause of permanent FEV loss (Table 5.8, p. 87).

Factors affecting mucus hypersecretion

Among the factors which were significantly related to mucus hypersecretion, indicated by mean phlegm score or mean sputum probit (Table 6.7), chest episode frequency was by far the most important, followed by measurements of ventilatory capacity, smoking habits, and the presence of radiological emphysema. Among the childhood illnesses (Appendixes, section A.8), only childhood catarrh and bronchitis were related. The correlation with age, although allowed for throughout Table 6.7, was weak: weight was related only to phlegm score.

Since the correlation between chest episodes and mucus hypersecretion appears to be due predominantly to mucus hypersecretion increasing liability to chest illnesses, we can ignore this correlation in looking for causes of mucus hypersecretion. The relationship between smoking and mucus hypersecretion is described in more detail in Table 6.8, where mean sputum volumes, mean sputum slopes, and mean phlegm scores are given for various categories of smoking. A general increase in mucus hypersecretion with amount smoked can be seen, as can the tendency for hypersecretion to decrease more in those who stop smoking than in those whose habits

Table 6.7. Multiple regression of mean expectoration from 1962–1969

F-ratios for the correlations of various factors with phlegm score and sputum probit given (a) age and (b) age and smoking habits (9 smoking groups). (See section B.15 of the Appendix for computational details and p. 74 for an explanation of F-ratios.) Regression coefficient for phlegm score are given in brackets.

	Phlegm score 0–4		Sputum probit	
	(a)	(b)	(a)	(b)
Smoking, 3 groups: none, light, 5 or more cigarettes/day	7·0***	—	41·0***	—
Cigarette smoking: daily amount given whether none, light or 5+ (0·03 per daily cigarette)	1·5*** (·03)	—	14·4***	—
Chest episode frequency†	23·0†*** (·83)	220·7†*** (2·67)	122·7***	111·7***
FEV (litres)	8·7*** (−·69)	59·2*** (−0·57)	72·4***	52·3***
FEV/H^3 (cl/m^3)	7·2*** (−·034)	53·6*** (−0·029)	77·4***	58·1***
FEV%VC	55·1*** (−·037)	34·6*** (−0·029)	51·3***	35·6***
VC (litres)	33·8*** (−·39)	26·6*** (−0·33)	27·0***	21·1***
X-ray emphysema	15·9*** (·52)	10·0** (0·47)	23·5***	17·9***
X-ray emphysema *given* FEV/H^3	6·3* (·38)	3·9* (0·29)	11·5***	9·2**
Childhood catarrh†	13·1†*** (·65)	13·1†*** (0·61)	4·9*	4·4
H. influenzae antibodies	9·3** (·36)	2·4 (N.S.)	6·5*	1·7
Childhood bronchitis†	5·4†* (·28)	6·0†** (0·49)	3·1	3·2
Weight (kg)	4·7* (−·09)	0·2 (N.S.)	0·0	0·9

There was no statistically significant correlation ($P < 0.05$) between any of the indices of mucus hypersecretion and any of the following factors: clinical asthma, other allergic diseases, other childhood illness, skinfold thickness, height, variability of FEV, nor, among smokers, frequency of use of filter-tipped cigarettes given type and amount smoked.

† Quantities assessed by questionnaire, which may give spurious correlations with phlegm score since this was also assessed by questionnaire.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

do not change so markedly. (Many of the irregular smokers smoked quite heavily at most surveys—see p. 81.)

After standardizing for smoking habits and age, we find (Table 6.7) that only the indices of airflow obstruction, emphysema, childhood catarrh, and childhood bronchitis remain correlated with phlegm

Table 6.8. Expectoration by smoking habits

The relationship between smoking habits and mucus hypersecretion. (This table estimates what would have been found if the original sample of men had not been stratified.)

Smoking habits (see section B.8 of Appendixes)	Mean phlegm score 1962–9	Mean sputum volume 1962–9 (ml)	100 × annual rate of change of sputum probit (relative to mean)	Percentage of men
Non-smokers	0·23 ± 0·12	0·30 ± 0·15	0·8 ± 0·7	10·3
Ex-smokers	0·41 ± 0·14	0·40 ± 0·17	−0·2 ± 0·8	14·4
Gave up in 1961–2	0·69 ± 0·33	0·54 ± 0·40	−3·2 ± 1·9	2·7
Pipe and/or cigar only	0·74 ± 0·26	0·37 ± 0·32	0·8 ± 1·5	4·7
5 or less cigarettes/day	0·85 ± 0·15	0·55 ± 0·19	−0·2 ± 0·8	12·0
Irregular: sometimes no cigarettes at all, but 1961–9 average > 5 cigarettes/day	1·06 ± 0·14	0·88 ± 0·18	−0·6 ± 0·8	13·1
Regular cigarettes 1961–9, mean 5–15 cigarettes/day	0·92 ± 0·11	0·75 ± 0·14	0·1 ± 0·6	23·8
Regular cigarettes 1961–9, mean 15–25 cigarettes/day	1·43 ± 0·14	1·15 ± 0·17	0·8 ± 0·8	14·3
Regular cigarettes 1961–9, mean > 25 cigarettes/day	1·59 ± 0·24	1·50 ± 0·30	−0·7 ± 1·4	4·8
All men	0·88 ± 0·05	0·72 ± 0·06	0·0 (necessarily)	100·0

score. Among the negative findings, perhaps the most interesting is the lack of any strong relationships with clinical asthma or other allergic diseases. All the correlations with sputum probit are weaker than with phlegm score, presumably because the latter is a more accurate index of mucus hypersecretion (Fletcher *et al.* 1974). Because of this, the correlations with phlegm score (i.e. with the annual questionnaire results) are in general more relevant than the correlations with sputum probit (i.e. with the expectoration measurements).

The only exception to this, as is noted in Table 6.7, are childhood catarrh and childhood bronchitis. These were themselves assessed by questionnaire and, since the questionnaire referred to events many years in the past, the answers will inevitably be somewhat inaccurate. Answers to questions about present phlegm will also be somewhat inaccurate, and presumably certain men will, relative to the average standard of reporting, tend to over-report both their past and their present mucus hypersecretion, or to under-report both. If this is true, strong correlations between phlegm score and childhood bronchitis and catarrh might well arise in the complete absence of any true correlation between past and present hypersecretion. For this reason, these four correlations in Table 6.7 are uninterpretable. Unfortunately, even the correlations of these childhood disorders

with sputum probit might be biased if men who now suffer from mucus hypersecretion are better able than those who do not to recall whatever catarrh and bronchitis they suffered as children. In the light of this probable bias (or even if it is discounted), the smallness of the F-ratios (1·5 and 3·0; not statistically significant) we actually observe for the correlations of childhood catarrh and bronchitis with mean sputum probit given age and smoking suggests that the correlation between *real* childhood hypersecretion and *real* adult hypersecretion is so weak as to be medically irrelevant, perhaps because adult hypersecretion is so dominated by smoking. The only escape from this conclusion would be to posit such gross inaccuracies in adult recall of childhood bronchitis that the answers given in adult life are almost uncorrelated with what actually happened in childhood, and we find this degree of inaccuracy implausible.

We have already discussed (p. 100) the relationship between low FEV and mucus hypersecretion, and we concluded that it was due not only to a common correlation with smoking but also to a common susceptibility of the large airways to mucus gland hypertrophy and of the small airways to obstructive changes and emphysema. If we are correct, then we would expect that given age, smoking, and the current extent of airflow obstruction, there would be little or no relevance of hypersecretion to mortality from obstructive airflow disease. (In clinically ill patients, mucus hypersecretion and attendant infective processes can precipitate fatal respiratory failure, but they have a negligible effect on the 20-year prognosis of a man who is as yet only moderately obstructed.)

Regressions on sputum probit slope

There was a highly significant correlation between 'cigarette regression' (see below) and sputum probit slope, which remained after all other factors had been adjusted for (F-ratio = 11·0 directly, or 10·3 given symptoms: $P \simeq 0{\cdot}001$), indicating that decreasing cigarette consumption decreased sputum production. The only other factor which was significantly correlated with sputum probit slope was a history of eczema in childhood ($P = 0{\cdot}02$). Since sputum tended to decrease in those with such a history, this is probably just a statistical fluke, since we examined about 50 correlations with sputum probit slope.

Cigarette regression

Since daily cigarette consumption rate was recorded at each summer survey, we could estimate the rate at which cigarette consumption

Table 6.9. Multiple regression of changes in cigarette consumption
Various correlations with cigarette regression 1961–9 given age and mean cigarette consumption 1961–9. (See Section B.15 of the Appendixes for computational details and p. 74 for an explanation of F-ratios.)

Factor	F-ratio	Significance	Regression coefficient
$\log(FEV/H^2)$	15·7	$P < 0{\cdot}001$	$\sim -0{\cdot}2$ daily cigarettes per year for each litre of FEV
Mean sputum probit 1962–9	7·3	$P < 0{\cdot}01$	$\sim -0{\cdot}05$ daily cigarettes per year for each ml of sputum
Any chest illnesses 1962–9 involving one week in bed and increased phlegm? (0 = no, 1 = yes)	11·7	$P < 0{\cdot}001$	$\sim -0{\cdot}3$ daily cigarettes per year

was altering during the study as the regression coefficient of the number of cigarettes smoked per day on calendar year (the 'cigarette regression'). Fifty-three men attended too few summer surveys to define a stable regression coefficient (see Appendixes, section B.4), and their rates of change were arbitrarily estimated to be zero. A quarter of the men never smoked cigarettes during the whole course of the study, and we therefore have meaningful rates of change for only 545/792 men.

There was a tendency for the rates of decrease of cigarette consumption to be larger in those whose average rates of consumption were highest. This is just a reflection of the national trend towards increasing numbers of ex-smokers with advancing age (Todd 1972, Tables 45 and 51): when a heavy smoker stops smoking, the reduction in his daily consumption rate is, of course, greater than when a light smoker stops. However, *given* current smoking habits and age, there was a tendency for those with symptoms of bronchitis (dyspnoea due to airflow obstruction, mucus hypersecretion, or recurrent illnesses) to decrease more than those without such symptoms (Table 6.9). The smallness of the regression coefficients probably indicates that the effect was erratic rather than that it was minute in those to whom it did apply, since few men had distressing bronchitic symptoms. The relationship with obstruction was discussed in more detail on p. 82.

Sputum purulence and phlegm score were also correlated with cigarette regression, but these correlations disappeared after adjustment for sputum probit. Rather surprisingly, the frequency of chest episodes was not significantly associated with the rate of decrease of cigarette consumption (although the regression coefficient was just over 1 S.E. away from zero in the direction of such a correlation). The only other factor which correlated with cigarette regression was

that people who were light in weight in 1961 tended ($P = 0{\cdot}02$) to smoke less in 1969 than in 1961, *given* smoking, age, and bronchitic symptoms. This may be a chance finding, as many minor factors were examined.

7 Discussion and conclusions

Summary

AFTER REVIEWING the validity of our techniques, we draw together our results to give an overall description of the various components of chronic non-specific lung disease, their interrelationships and causes. Two main disorders are involved, the obstructive disorder, which may lead to progressive disability, respiratory failure, and death, and the hypersecretory disorder, which may sometimes accompany the obstructive disorder but which is of itself of much less significance. Recurrent clinical chest infections are promoted by the hypersecretory disorder, but do not themselves cause any obstructive changes.

Each disorder is chiefly caused by smoking, but smoking has an appreciable effect only on men who are susceptible to one or both of them. Susceptibility to one disorder correlates (but is not identical) with susceptibility to the other. However, many obstructed men have little or no mucus expectoration, while many with chronic expectoration will never develop significant obstructive disease. In middle age the extent to which the obstructive disorder has already developed can be used to predict future disability and mortality, while, given the degree of obstruction already present, the extent to which the hypersecretory disorder has developed cannot.

The obstructive disorder is thus of primary interest. If a 'susceptible' smoker, who is losing FEV more rapidly than if he were not smoking, gives up, his lost FEV is not recovered but his subsequent rate of loss is likely to be shallower than if he had continued to smoke, and his expectation of non-disabled life is thus improved. We discuss possible future lines of research in obstructive lung diseases, and conclude that, apart from developing better means of preventing smoking, the most important thing is to investigate the constitutional or environmental factors that determine which smokers are most susceptible to the development of significant airflow obstruction, rather than spending any further effort on studying expectoration.

The validity of the methods used in the study

The sample of men

It must be re-emphasized that the study was not concerned with

the various clinical syndromes associated with airflow obstruction that are severe enough to lead patients to seek medical advice. It was designed to investigate the way in which obstruction starts to develop in men who are still fit enough to remain in full-time employment. It was therefore appropriate to study working men, but the Follow-Up Group we studied was neither a random nor a representative sample of any defined population. The initial stratified sampling scheme increased the proportions of men with expectoration and also of non-smokers, but correction was made for this particular distortion in the analysis (Appendixes, section B.7). It was also appropriate to exclude the small number of men with diseases other than bronchitis, emphysema, or asthma which might have affected lung function. The fact that most of the men who already had severe airflow obstruction in 1961 were either already absent from the works population or lapsed by death or retirement during the study was inevitable and is immaterial to a study which was almost wholly concerned with preclinical disease in men well enough to continue at work for several years.

It is probable that our findings are of general relevance to the early stages of the development of chronic obstructive lung disease in middle-aged males, because the interrelationships found at the initial (1961) survey between the main variables, smoking habits, sputum volume, chest illness frequency, and FEV level were similar to those found in other prevalence surveys.

Assessment of airflow obstruction

In routine clinical assessment of lung function, FEV%VC is generally measured to distinguish between restrictive reduction of FEV, in which the index is normal or high, and reduction of FEV due to airflow obstruction, in which it is low. At the beginning of the study, we measured only FEV because VC was regarded as having poor reproducibility and restrictive diseases were considered too rare to affect our results. Later in the study we also measured VC and in the early reports of our study we used low FEV%VC as an index of airflow obstruction. In the present analysis, however, we have made little use of FEV%VC since we have excluded the 25 men (3 per cent) who had conditions other than chronic obstructive lung disease, which might reduce FEV. The only value that FEV%VC might have had would have been as a means of standardizing FEV for physique but, for the reasons given in section B.6 of the Appendixes, we found FEV/H^3 (H = standing height) was preferable for this. The FEV is, of course, an insensitive index of minor degrees of small airway narrowing or emphysema (Macklem 1972) but since no-one

develops a disabling degree of airflow obstruction without gross loss of FEV, the rate of decline of FEV (FEV slope) is a valid (although somewhat inaccurate) index of the rate of progression towards this condition during our study.

The steps we took to improve the accuracy of FEV, and thus of FEV slope, are described in detail in the Appendixes, sections B.1–B.5 but are, for convenience, summarized here. First, we discarded readings taken when any man was receiving bronchodilator drugs and readings which the observer reported as being influenced by poor co-operation or other factors (such as a spinal jacket or recent dental extraction) which prevented full inspiration or maximum forced expiration. Next, we used only the maximum of the last three of the five FEV readings taken at each survey, since this was more reproducible than the mean (section B.1). These FEV readings were then corrected for observer biases and secular effects (section B.2).

The measurements at the later surveys were less variable than those at the earlier surveys, perhaps because of a training effect; the mean FEV level for each man was therefore calculated as a weighted average of all the corrected FEV measurements made on that man, the later measurements getting slightly greater weights than the earlier ones (Appendixes, section B.4). (The weighted average never differed from the simple average by as much as 0·01 litres.)

Assessment of the rate of development of airflow obstruction

The mean annual rate of loss of FEV (FEV slope) for each man during the course of our study was derived as follows: we omitted any of his corrected FEV measurements which, after standardization by 30 ml/year to 1965, were more than ±450 ml away from his mean FEV level ('winsorization'), calculated the regression coefficient of corrected FEV (Appendixes, section B.2) on calendar year, and subtracted 15 ml/year from it. In discussions with other epidemiologists, it has become clear to us that the two ways (winsorization and subtraction of 15 ml/year) in which our FEV slopes differ from simple regression coefficients make people feel much less at ease with our statistical analysis than they would if simple regression coefficients had been used. It is more difficult to allay unspecified misgivings than to discuss particular biases, but it is important that our results are not unjustifiably doubted or dismissed. In the next two paragraphs we show that winsorization could not have distorted our findings and that subtraction of 15 ml/year is irrelevant to all our multiple regression and least-squares analyses.

The chief worry about winsorization seems to be that although only a very small proportion of the FEV readings were lost, nevertheless

the lost data points might be those associated with the most interesting events of all, very steep slopes or sudden, large FEV changes. This is not, in fact, the case. Visual examination of the FEV data for the men with the steepest and shallowest FEV slopes shows only one man in the whole study whose slope was inappropriately altered by winsorization (Appendixes, Chart F.2). Inspection of every man with two FEV readings six months apart that differed by over 0·75 litres (Appendix C) showed that the winsorized slopes appear visually to describe the data much better (see, for example, Charts F.14 and F.15 in the Appendixes). Finally, we know for certain that we would have got the same qualitative answers from our regression analysis anyway, because we originally *did* the whole analysis before winsorization occurred to us! When we repeated this analysis using winsorized slopes, the only substantial difference was a reduction of the standard errors of mean FEV slopes in certain groups of men.

Subtraction of 15 ml/year from each man's FEV slope made the mean FEV slope of the men in the Follow-Up Group −45 ml/year. This was done for three reasons. First, because the decrease of variance of FEV in the second half of the survey indicated that improvements in FEV technique were occurring which meant that our mean FEV slope underestimated the real rate of loss of FEV in the course of the study by 10–20 ml/year (Appendixes, section B.3). Secondly, because the regression of FEV on age was −46 ml/year (Table 3.12); and thirdly, because two other prospective studies in British men of changes in FEV over periods of five and nine years observed rates of decline of FEV of about this magnitude: −47 ml/year in non-miners aged 55–64 in Wales (Higgins and Oldham 1962), and −45 ml/year in miners and non-miners aged 55–64 in Staveley (Higgins *et al.* 1968). Subtraction of 15 ml/year has no effect whatever on any of our subsequent calculations (correlations, multiple regressions, calculation of S.E.s etc.) except for tabulations in Chapter 5 of mean FEV slopes in which tabulations each mean FEV slope is exactly 15 ml/year steeper than it would otherwise have been. This in turn affects the forecasts of the future development of disability in relation to present FEV level which are developed later in this chapter. Although we cannot be sure that subtraction of 15 ml/year from the various mean FEV slopes is exactly correct, something of this order is probably appropriate. The *differences* between the mean FEV slopes in different groups of men are not, of course, affected by our choice of what, if anything, to subtract.

These several adjustments of our FEV data may make direct comparison of certain details of our results with those of other studies difficult or impossible. For this reason, and because further analyses

of our data may be of interest to future research workers, a public copy of our original data is available on magnetic tape at Oxford University. Alternatively, we will gladly supply card listings of any particular items that other research workers want to analyse differently. Correspondence should be addressed to R.P.

Indices of bronchial infection

These indices were designed to assess the frequency and severity of the types of chest infection which have been thought by many clinicians and pathologists to be causes of emphysema or of irreversible bronchiolar narrowing and obliteration.

Since chest episode frequency (ignoring multiple episodes within a single six-month period) was our main index of bronchial infection, we need to know how far these reported episodes were due to or associated with bronchial infection. In the detailed study carried out in the winter of 1962–3 (Angel *et al.* 1965), purulent sputum was observed during the week of onset of 33 per cent of the episodes and was reported, but not confirmed by sputum examination, in a further 29 per cent. *H. influenzae* and/or *Streptococcus Pneumoniae* were cultured from just under 40 per cent of sputum specimens taken at the times of these episodes, compared with 21 per cent of specimens taken between episodes. It seems probable that an increase of bronchial infection occurred in at least half of the episodes. Since each man has been asked about these episodes many times over, our estimates of the frequencies were probably quite accurate.

Our assessments of sputum purulence were unsatisfactory. They were relevant only to a short period before each survey, they might have been subject to considerable observer variation (p. 65), and they may have been related to nasal as well as to bronchial infection. Our recording method forced the continuum of purulence into artificial Yes–No categories and could not assess purulence in men who failed to return sputum specimens, thereby creating an unwanted association of purulence with sputum volume. Because of these drawbacks, particularly the last, we have been unable to make much use of this index of infection.

Our assays of antibodies to *H. Influenzae* are also unsatisfactory. They were done only once, the results were not quantitative, and little is known about the time relationship of *H. Influenzae* infection in the bronchi and appearance of these antibodies. It is rather perplexing that chest episode frequency is uncorrelated with *H. Influenzae* antibodies or, after allowing for expectoration, with sputum purulence, although antibodies and purulence were correlated with each other. Furthermore, *H. Influenzae* antibodies and sputum purulence

correlated directly with smoking habits rather than with expectoration, while the opposite was true of chest episode frequency. We believe that this indicates that chest episodes represent a process which is largely unrelated to the determinants of *H. Influenzae* antibodies, but an alternative explanation might be that something is seriously wrong with one or other of our indices of infection.

We have no direct assessments of asymptomatic bronchial infections which might be relevant to irreversible damage to the small airways and alveoli, but since there is evidence that hypersecretion of mucus is usually associated with bronchial infection in subjects without other respiratory symptoms (Lees and McNaught 1959; Laurenzi *et al.* 1961), we can reasonably assume that such infection is more likely to be present in men with than in men without expectoration, and we can thus use expectoration as an indirect index of asymptomatic infections.

In summary, we have not assessed asymptomatic infections at all well, but we have assessed reasonably well the frequency (although not the severity or the causative organisms) of symptomatic infective events.

Measurements of mucus hypersecretion

We know of no means whereby the total volume of mucus secreted in the bronchi can be measured. All that can be done is to assess the amount of sputum which is expectorated. In normal bronchi, mucus secretion is always in progress,† and it is usually assumed that the normal secretion rate must be greatly exceeded before some of the increased production is expectorated as sputum instead of being swallowed unconsciously. We can be fairly sure that the men who had regular expectoration had definite mucus hypersecretion and that they had more mucus hypersecretion than men who did not expectorate. An unknown number of the latter men may, however, have had mucus hypersecretion of a degree insufficient to cause expectoration. Particularly, substantial changes in the tiny amount of mucus normally secreted in the small airways could occur without any appreciable effect on expectoration, since expectoration is chiefly determined by the amount of mucus secreted in the larger bronchi.

Measurements of expectorated mucus can never be accurate. We were at first confident that measurements of morning sputum volume would be more useful and reliable than answers to questions about

†The normal amount of secretion is often said to be about 100 ml/day (Policard and Galy 1945) on the very uncertain basis of a mg per kg body weight extrapolation from tracheostomized rabbits and cats (Perry and Boyd 1941), but it seems intuitively unlikely that it can really be as great as this.

expectoration and we took great care to make these rather tedious measurements as accurate as possible. But it turned out that a better index of mucus hypersecretion could be derived from a five-point score based on the much simpler technique of asking questions about phlegm production (Fletcher *et al.* 1974). These questions were originally validated by their relationship to sputum volume and FEV level (Fletcher *et al.* 1959) and have now become internationally adopted (World Health Organisation 1975).

Although the phlegm score was designed to maximize the correlation with FEV level, and this might result in spurious positive correlations between these two variables, this increases the reliability of the lack of any correlation between this score and rate of decline of FEV which we actually found (Appendixes, section B.8). False correlations may arise between phlegm score and other indices such as chest episode frequency which are also assessed by answers to questions, because some individuals may be predisposed to over-report any symptoms. For this reason, it is desirable to have two independent measures of mucus hypersecretion—questions and sputum measurements—and to obtain, as we have done, confirmatory negative and positive correlations of both indices with other factors.

The nature of the airflow obstruction found in our study

The absence of any morbid anatomical studies of the men who had airflow obstruction makes discussion of its anatomical basis a matter of assumption and conjecture. It is reasonable to describe it as 'irreversible airflow obstruction' (Ciba Guest Symposium 1959) for two reasons. First, because in only one case did it remit (Appendixes, Chart F.14) and secondly because in the autumn of 1963 we measured FEV before and after isoprenaline inhalation in the men who had taken part in the special study of illnesses that year (Angel *et al.* 1965). At that time, 21 of these men had values of FEV/H^3 below 55 cl/m^3. Their mean FEV was 1·71 litres before and 1·80 litres after inhalation of isoprenaline—an increase of only 0·09 litres, or 5 per cent. The four men who had the greatest increase of FEV on isoprenaline had a mean FEV of 1·69 which rose to 1·96, an increase of 16 per cent. This sort of increase of FEV on inhalation of isoprenaline is typical of patients with chronic obstructive lung disease and is much less than would be expected in patients with asthma of similar severity.

Twenty-five per cent of the men with definite loss of FEV ($FEV/H^3 < 55$ cl/m^3) denied phlegm production at all times during the study and 30 per cent of them never produced any sputum

(Table 5.13, p. 95; these figures have been corrected for the effects of the 1961 stratification). Many might assume that these men had emphysema, but the absence of mucus hypersecretion as shown by expectoration does not necessarily exclude intrinsic disease of the airways (Matsuba and Thurlbeck 1973).

A laboratory study of a small group of men with significant obstruction (Appendixes, section E.1) suggested that both emphysema and intrinsic disease of the airways were involved to differing degrees in these men. This seems in any case likely, since both of these pathological processes are related to smoking and are closely associated in autopsy studies (Matsuba and Thurlbeck 1972; Scott 1973, 1976). That emphysema was making a significant contribution to airflow obstruction in our study is shown by the correlation between radiological emphysema and FEV level (Table 5.17, p. 103).

Factors that cause irreversible airflow obstruction

Smoking

In conformity with virtually all prevalence surveys and clinical reports, our study has confirmed that cigarette smoking is now the main cause of chronic airflow obstruction. But smoking leads to airflow obstruction of a degree which is likely to have any functional or clinical importance only in a minority of smokers, who must therefore have some special susceptibility to the effects of tobacco smoke on the lungs.

Table 5.6 on p. 83 shows that only a sixth of the smokers in our study had values of FEV/H^3 less than 50 cl/m^3 (corresponding to an FEV below 2·5 litres in a man of height 1·71 m). The mean FEV slope of these 'obstructed' smokers was twice as steep as that of ex-smokers, whereas the less obstructed smokers had a mean slope which was only slightly greater than that of non-smokers or ex-smokers. The figures given in Table 5.6 suggest that the effect of smoking on FEV level has often been underestimated in prevalence studies where, as is usual, mean FEV levels of smokers (grouped according to tobacco consumption) are compared with each other and with those of non-smokers. In such comparisons, the real effect of smoking on FEV among a susceptible minority of smokers† is concealed by the virtually normal FEV levels of the majority. In addition to this, the index of exposure to tobacco smoke usually employed in epidemiological

† We are not necessarily positing that 'susceptibility' is an all-or-nothing characteristic, but we are suggesting that if the whole population were exposed to (say) 15 cigarettes/day for 30 years, the resultant FEV losses would have a skew distribution, with many quite small losses but a 'tail' of clinically significant losses. This is confirmed by the skewed distribution of the amount of emphysema measured at autopsy among 106 smokers by Ryder *et al.* (1971).

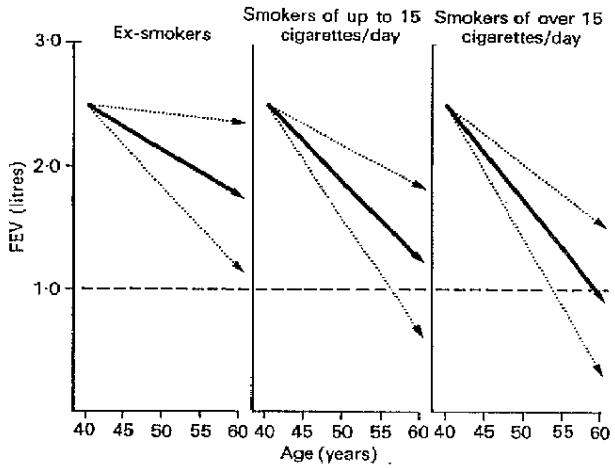


Fig. 7.1. The effect of stopping smoking at age 40 on subsequent losses of FEV

The Figure illustrates the FEV losses we would expect to find over a 20-year period in 3 groups of men who had all smoked the same amount as each other until the age of 40, developing definite, but mild, airflow obstruction (FEV = 2·5 litres) because of this. One group then gives up smoking at age 40, one group smokes under 15 cigarettes/day thereafter, and one group smokes over 15 cigarettes/day. The dotted lines represent trends about 1·5 S.D. above and below the mean trends. The dashed horizontal line indicates an FEV of 1·0 litres, which is normally associated with disability.

Twenty-year extrapolation of an *individual* slope observed over 8 years would be quite unjustified in view of the large errors of estimation of true individual slopes. It is more reasonable to extrapolate mean slopes appropriate to a particular FEV level, especially since, given FEV level, age is irrelevant (Appendixes, section B.9). The effect on these predictions of the acceleration of FEV loss will not be appreciable (Table 4.6, p. 67).

The extrapolation in Fig. 7.1 is, of course, based on the assumption that subtraction of 15 ml/year from the slopes gives the true mean slope of any group of men. It is also based on the assumption that all other factors which may affect FEV slope (e.g. air pollution) remain constant over the coming 20 years and that smokers do not start using modified cigarettes which are less harmful to their lungs than those which they have hitherto smoked.

studies is the current level of smoking. We have found a tendency for smokers with reduced FEV levels to reduce their cigarette consumption more than those with higher levels (Table 5.5; p. 82). This is probably the reason why in most prevalence studies, including our own initial survey (Table 3.15; p. 48; and Fig. 3.3, p. 48), only a small difference of FEV level between lighter and heavier smokers has been found. Some authors have tried to deal with these changes in consumption by calculating 'lifetime' cigarette consumption (p. 78), using an index such as 'pack-years', but such indices are prone to severe inaccuracies owing to the poor recollection that smokers have of their previous habits (Todd 1966).

None of the lifelong non-smokers in our study had 'airflow obstruction' (defined as FEV/H^3 < 50 cl/m^3 *and* FEV%VC < 67), and the absence among them of a significant correlation between FEV level and slope (Appendixes, Table B.8) indicates that the variation of FEV level among them was due much more to differences in physique than to differences in rates of loss of FEV. In autopsies, lifelong non-smokers are found, almost without exception, to be free from significant emphysema or small airways disease (Anderson *et al.* 1972; Auerbach *et al.* 1972, 1974; Thurlbeck *et al.* 1974). In clinical series, a small minority of patients with severe irreversible airflow obstruction are reported to be lifelong non-smokers. Some of these may be ex-smokers who wish to conceal their former smoking habits, some may have undiagnosed intrinsic ('late onset') asthma (Scadding 1971), some may have an exceptional susceptibility to general or occupational air pollution from α_1-antitrypsin deficiency or may have some unrecognized idiosyncratic types of illness. The important thing is that, in epidemiological terms, lifelong non-smokers with severe airflow obstruction are great rarities. Clinical study of such individuals may be illuminating but their existence should not divert attention from the dominant role of cigarette smoking in the present-day aetiology of disabling airflow obstruction.

Effect of giving up smoking. Our finding, in agreement with that of Comstock *et al.* (1970), that when smokers who already have definite airflow obstruction stop smoking their accelerated decline of FEV slows down so that their FEV slope becomes, on average, the same as that of non-smokers, is important from the point of view of prevention. The possible importance of this observation is illustrated in Fig. 7.1, which provides a 20-year linear extrapolation of the mean rates of decline ($\pm 1\frac{1}{2}$ S.D. of true decline rates, estimated† as $\pm$20 ml/year) which we observed in ex-smokers and in moderate and heavy smokers, as they would apply to men who have smoked until aged 40, 171 cm in height with an FEV of 2·5 litres (FEV/H^3 = 50 cl/m^3). By the age of 60 only about 5 per cent of those who had stopped smoking at 40 would have an FEV below 1 litre, while a third of those who had continued to smoke less than 15 cigarettes/day plus more than half of those who smoked more than this would have an FEV of less than a litre and would probably be severely disabled. Whatever the appropriate S.D. may be, about half of each group of

† It is difficult to know the S.D. of real rates of decline in obstructed men, let alone the dependence of S.D. on smoking habits. The S.D. in obstructed men will be greater than the $\pm$15 ml/year estimated (Appendixes, section B.11) in all men, but Table B.8 suggests that it will not exceed $\pm$20 ml/year.

men will do better than average for that group (solid arrow), while half will do worse.

The chance of survival and freedom from disability is clearly much greater for those who have stopped smoking. This improvement of prognosis is endorsed by the major prospective studies of mortality rates in relation to smoking habits (Doll and Hill 1964; Best 1966; Kahn 1966; Hammond 1966) in which ex-smokers have been found to have much lower mortality rates ascribed to bronchitis and emphysema than cigarette smokers who have continued to smoke. The conclusion that there are improved prospects for those who give up smoking is also supported by pathological studies which have shown much less severe emphysema in ex-smokers than in continuing smokers (Auerbach *et al.* 1963).

In spite of this evidence, many people have taken the view that once the lung has been damaged by smoking, progression of the disorder is unaffected by stopping smoking (Macklem *et al.* 1974). This view has been based on reports that in *clinical* series of patients with chronic obstructive lung disease, patients who stop smoking do not have a better prognosis than those who continue to smoke (Jones *et al.* 1967; Burrows and Earle 1969). Among clinical series of patients, however, those who stop smoking tend to have stopped because they have even more advanced disease than those who continue: the gravity of their disease then determines their prognosis. Such observations, made in the terminal stage of the disease, do not contradict our evidence that stopping smoking while lung function is only moderately impaired is, on average, of great benefit. We did not detect any differences in mean FEV slope between smokers of filter-tipped and plain cigarettes. Filter-tip users, however, are self-selected, and may have different manners of smoking or different susceptibilities to disease. Ours is not a controlled study demonstrating filters to be without effect.

Other causes

Our study provides no information about the part played by general or occupational air pollution in causing irreversible airflow obstruction, for none of our sample of men were exposed to any recognized injurious dust or fumes and all lived in a similar urban environment. During the period of our study levels of air pollution in London were declining steeply (Fig. 4.6, p. 63). At one time, we thought that the difference between the observed mean FEV change of −30 ml/year in the Follow-Up Group and that of −45 ml/year which was expected from the regression of FEV on age was due to the beneficial effects of this decline in pollution. We now realize that this difference could be

spurious and due only to the depression of some early readings by the cold winter of 1961–2 and to increasing competence in the performance of the FEV test during the course of the study (Appendixes, section B.3).

There are undoubtedly causes of chronic obstructive lung disease on which our study can throw no light, some of which were presumably responsible for the high 'bronchitis' mortality in the United Kingdom long before cigarette smoking began (Collis 1923). The large social-class gradient of 'bronchitis' mortality in England and Wales, for example, was present before any social-class gradient in cigarette consumption had appeared.

Factors that do not cause irreversible airflow obstruction

Bronchial infection

We have concluded that symptomatic bronchial infection was not a cause of persistent airflow obstruction in our sample of men. We have great confidence in this conclusion because of the strength and consistency of our negative evidence. None of our indices of infection correlated with FEV slope after adjustment for FEV level and there was no evidence that the chest episodes we observed had any permanent effect on FEV level (Table 5.11, p. 91). We also consider that this conclusion is of general validity because we have found no published observation to support the widely held belief (*British Medical Journal* leading articles 1973, 1976; Hallett 1973; Crosby 1974) that acute infective exacerbations of chronic obstructive lung disease may cause a permanent loss either of FEV or of any other index of ventilatory capacity. In patients with severe airflow obstruction, a slight reduction of FEV is often seen when an exacerbation of infection occurs (Howard 1967), but such losses are usually only temporary (Felix-Davies and Westlake 1956). Although Howard (1967) reported a few sudden losses of FEV in bronchitis patients attending hospital, a later repetition of his study (Howard 1974) on a similar series showed no such effects.

Apart from the above cases, the view that clinical infections cause permanent obstructive damage appears to be based on three inadequate pieces of evidence:

1. There is a correlation between low FEV and frequent chest infections, but this correlation exists chiefly because both are associated with mucus hypersecretion (Table 6.1, p. 107).
2. Some patients give a misleading history (see, for example, Chart F.1, in the Appendixes), suggesting that their respiratory disability dates back only to an acute respiratory infection.

3. At autopsy, there is an association between obstructive lesions and inflammatory processes; however, the inflammatory processes are not necessarily related to clinical (or even to subclinical) infections, and, even if they were, association need not imply causation.

We cannot, of course, say that no clinical infection ever causes an appreciable degree of irreversible airflow obstruction, but we can assert that this must be a rare event in adult life. There are two conditions, prevalent especially in children and young adults, in which it has seemed probable that infection causes airflow obstruction. The first is cystic fibrosis. In this disease, severe bronchial infection is almost invariably present, so that it is difficult to compare children with and without infection in whom the disease is otherwise of uniform severity, and it may well be that liability to develop obstruction is as much a direct result of the disease as is liability to infection. Bronchiectasis is the other condition which is often associated in young people with airflow obstruction. In this condition, it seems to have been assumed that the infection and hypersecretion of mucus are the cause of associated airflow obstruction (Thurlbeck *et al.* 1970), but this view is again based on the assumption that association implies causation. In 1974, Landau *et al.* reported a long-term follow-up of pulmonary function in young subjects with bronchiectasis in which records had been made of the frequency and severity of infective episodes. Although the paper does not relate this to rate of reduction of FEV, Dr. Landau has reported, in a personal communication, that there was no such relationship.

Although acute symptomatic infections do not cause irreversible airflow obstruction, there remains the possibility that subclinical infections may do so, just as symptomless bacteriuria may cause chronic renal damage (Kass and Zinner 1969), but the parallel between the renal tract and the bronchial tree is not close. In subjects without sufficient mucus hypersecretion to cause a chronic productive cough, the bronchi have usually been reported to be sterile, so that 'subclinical' bronchial infection appears only to occur in subjects with marked expectoration (Lees and McNaught 1959; Laurenzi *et al.* 1961). Since we found that mucus expectoration is not associated with significant loss of FEV, no viral, mycoplasmal, nor bacterial infections which are strongly associated with overt mucus expectoration can be significant causes of progressive airflow obstruction. Nor could any subclinical infections which are strongly associated with the frequency of clinical infections be causal. A causal role can be postulated only for some hypothetical subclinical infections which are unrelated to mucus expectoration, to clinical chest

episodes or to the production of *H. Influenzae* antibodies, and we know of no evidence that such infections occur, let alone that they are more harmful than clinical infections or than subclinical infections which are associated with mucus expectoration.

Allergy

Our indices of allergy are imperfect, but the complete lack of correlation of FEV level or slope with a personal or family history of allergic disorders, with variability of FEV readings, or with hyperreactivity to the inhalation of cigarette smoke provides no support for the hypothesis that allergy plays an important part in progressive loss of FEV. However, sputum eosinophilia was weakly correlated with steep FEV slope and low FEV, and the 17 men in the Follow-Up Group whom we considered (Appendixes, section E.2) to have clinical evidence of asthma had a steeper mean FEV slope and lower FEV than the rest of the Follow-Up Group, which suggests that they may have had a more rapidly progressive form of airflow obstruction. The difference in FEV slope was 22 ml/year (Table 5.16, p. 101), which is significant from the point of view of the asthmatic individual, but not from the point of view of the general population, since most people are neither clinically nor subclinically asthmatic. In our Follow-Up Group, for example, the mean FEV slope was only made 0·5 ml/year steeper by the asthmatics, and this is negligible.

The relationship between mucus hypersecretion, as indicated by expectoration, and low FEV

We have measured only mucus *expectoration*, either at the time of each survey (the sputum volume coughed up into a specimen bottle during the first hour in the morning), or during the year preceding the survey (scoring answers about usual phlegm during the preceding winter). Expectoration might not correlate with hypersecretion by the goblet cells, nor with the average amount of mucus actually present in the airways. (For example, in status asthmaticus expectoration may be absent despite severe airflow obstruction due to retained mucus.) Our measures of expectoration therefore only directly assess hypersecretion by the mucus glands.

As expected, a definite correlation between low FEV/H^3 and mucus expectoration existed, which at least validates our measurement techniques. The relationship was not precise (correlation coefficient = 0·3), and there were many individual exceptions to it (Table 5.13, p. 95). However, it was far from negligible: the regression coefficient was 2 cl/m^3 of FEV/H^3 (about 0·1 litres of FEV) per ml of expectorated morning sputum. This correlation

persisted after adjustment for smoking, so comparing two men with identical smoking habits, we would tend to find that the man with lower FEV had more expectoration.

This correlation is not due to chronic mucus hypersecretion directly increasing the rate of permanent loss of FEV in the past, because indices of expectoration are not correlated with FEV slope after adjustment for FEV level. It might therefore be postulated, as we have done previously (Fletcher 1975) that excessive mucus in the airways obstructs the flow of air in them but does not damage the airways or alveoli causing progressive airway narrowing or emphysema, but this hypothesis is not consistent with the temporal relationships between changes in expectoration and of FEV.

Using each man as his own control, it is possible to compare his FEV when he had a high sputum volume with his FEV when he did not, and likewise to compare his FEV losses in the years during which he reported usual phlegm with his FEV losses in other years. If mucus hypersecretion caused obstruction to airflow or permanently damaged the airways, we could detect this effect by examining surveys when expectoration was greater and at these surveys, we would expect the FEV level to be temporarily depressed or the FEV losses to be greater than that man's average. This was not found to be so (Tables 5.14 and 5.15 on pp. 97 and 99).

We therefore have to postulate that the association between expectoration and reduction of FEV is due to their having some common cause. This cannot be one which varies, causing more FEV loss and expectoration when it is more active, because of the lack of correlation between short term changes in both factors, so it must be some fairly constant common cause.

The correlation between expectoration and FEV slope shows that the common cause does not result merely in a non-progressively lower FEV, but causes steeper FEV slope in adult life. If the observed correlations between expectoration and FEV slope operated for 35–45 years, which is plausible if they represent an invariant common liability to expectoration and to FEV loss, then a correlation of the necessary strength would arise between expectoration and FEV/H^3. Thus, to explain everything we have observed, there is no need to postulate any further mechanisms other than this special susceptibility in certain individuals to both expectoration and more rapid FEV loss.

What might this common, lifelong determinant of lifelong susceptibility (in the polluted and cigarette-smoking conditions of working-class London) to expectoration and to steep FEV slope be? We have no data, and can only speculate. Analogy with the profuse hypersecretion and rapid FEV loss in α_1-antitrypsin deficiency suggest some aspect of macrophage lysis, contents, or removal might be worth investigating, and the British social-class gradient with respect to bronchitis suggests that some aspect of childhood environment, childhood nutrition, or childhood infection might also be.

Our conclusion that mucus expectoration, and the processes that are more active when it is increased, are not causes of either temporary or progressive airflow obstruction conflicts with the widely accepted idea that, because expectoration is an essential component—indeed, the defining characteristic—of 'simple chronic bronchitis' it is an essential precursor and component of 'chronic obstructive bronchitis'. Our data show this to be mistaken: expectoration and obstruction are best thought of as separate processes, with no connection between them other than a common susceptibility to develop both in the presence of cigarette smoking and the London environment.

For this reason, indices of mucus expectoration might help to single out young subjects, at present still fit, who have an increased chance of developing disability (Fletcher *et al.* 1959; Reid 1970). By middle age, however, chronic expectoration should not be as good an indicator of such people as some measure of the extent of FEV-reducing changes already present in their lungs would be, and this is what is actually found. Krueger *et al.* (1970) reported increased mortality in people with persistent cough and phlegm, but others have shown that this increased risk in people with productive cough disappears after allowing for dyspnoea (Higgins and Keller 1970) or for FEV level (Cole 1975).

The irrelevance of expectoration to chronic airflow obstruction is so much at variance with our own preconceptions and those of others that confirmation by other studies is needed. Cullen *et al.* (1970) and Scott (1973, 1976) found no correlation of mucus gland enlargement with emphysema at autopsy. Ryder *et al.* (1971) did find such a correlation, but many examples were found of marked emphysema without undue mucus gland enlargement and marked enlargement without emphysema. Their findings led them to conclude, as we do, that emphysema is not directly caused by mucus gland hyperplasia, but rather that the two conditions are both influenced by a common aetiological agent. They observed a highly skew distribution of the amount of emphysema per lung, many lungs having less than 10 per cent of emphysema while the amount of emphysema present in lungs with more than 10 per cent was very various. This conforms excellently with our inferred skew distribution of the susceptibility to develop airflow obstruction in response

to smoking, but almost all of their patients who were known to be smokers died in hospital and, if some of these deaths were due to emphysema, their contribution to the skewness is an artefact.

No other prospective study as big as ours has been reported, but Higgins *et al.* (1968) observed a random population sample of 320 young men and 237 middle-aged men twice, at an interval of nine years. Their FEV was measured, and questions about smoking and chronic phlegm production were asked. Given the mean FEV, and smoking habits the correlation of the difference between the two FEV readings (equivalent to our FEV slope) with the average of two scores derived from the answers to phlegm questions (equivalent to our phlegm score) was zero in the young men, but differed from zero by 2·48 S.E.s in the older men, in the direction of those with more phlegm having on average a greater loss of FEV (T. J. Cole 1975, personal communication). Their survey is smaller than ours, but this value does not coincide with our precisely negative results. However, in view of the inadvertent correlations that can arise between the means and differences of two FEV measurements, no undue discrepancy exists, and we must now await the findings that will emerge from large American and Dutch follow-up studies which have been started.

Causes of bronchial infection

We are concerned here not with the bacterial or viral agents which are responsible for persistent or recurrent bronchial infection (which we did not study), but only with those factors which we found increased the susceptibility to such infections. Since the actiological factors implicated in the chest colds or chest illnesses which were reported appear to be different from those implicated in the production of *H. Influenzae* antibodies or asymptomatic purulent sputum, these must be considered separately.

Factors affecting chest episode frequency

The main factor causing an increased liability to report chest episodes is mucus hypersecretion. Since our definition of a 'chest episode' required the existence of an increase of phlegm at the time of the 'episode', some correlation between mucus hypersecretion and chest episodes must necessarily exist. But inclusion of the 20 per cent of chest episodes which were not associated with an increase in phlegm did not materially change the strong correlation of these episodes with mucus hypersecretion. A correlation between mucus hypersecretion and chest illnesses has been observed in prevalence surveys, but in

such studies it has not been possible to discover which causes which.

Our prospective study has enabled us to observe that since no permanent increase in mucus hypersecretion occurs after chest episodes, the correlation is probably due to mucus hypersecretion increasing liability to chest episodes rather than the reverse, although our sputum volume measurements are so inaccurate that they are a rather shaky foundation for such a major conclusion. Stronger evidence perhaps is that the correlations of chest episode frequency with smoking and with airflow obstruction are almost extinguished by adjustment for mucus hypersecretion, while the converse is not true: the associations of phlegm score with smoking and with airflow obstruction are not much reduced by adjustment for chest episode frequency. After adjustment for mucus hypersecretion, only a small residual correlation of chest episode frequency with airflow obstruction remains. Even this may be due not to men with obstruction being more liable to chest episodes, but rather to their being more likely to report minor episodes with an associated increase in dyspnoea which would have so little effect on more normal men that they would discount and forget them.

The fact that, after adjustment for mucus hypersecretion, there is no correlation between chest episode frequency and smoking habits is an important negative finding. It indicates that tobacco smoke does not directly increase liability to acute bronchial infections but only causes the mucus hypersecretion which then increases this liability. It also confirms our conclusion that chronic mucus hypersecretion predisposes to clinical chest infections rather than the converse. The observation that among the men who deny phlegm production (Fletcher 1965) or return empty sputum bottles (Table 3.16, p. 49), smokers more often report chest illnesses than do non-smokers may be explained by the inaccuracy of 'persistent phlegm production' at a *single* survey as a quantitative index of mucus hypersecretion. Smokers who deny phlegm or fail to produce any sputum probably have more real mucus hypersecretion than non-smokers who deny it and this difference, rather than smoking itself, may be responsible for the increase in illnesses reported by these smokers.

Factors affecting H. Influenzae antibodies

Mucus hypersecretion is independently, though not strongly, related to the occurrence of *H. Influenzae* antibodies. The most important factor correlated with *H. Influenzae* antibodies is smoking, although smoking is not correlated with sputum purulence given mucus hypersecretion. We do not know why, given mucus hypersecretion, smoking should correlate with *H. Influenzae* antibodies but not with

sputum purulence or chest episodes (May *et al.* 1973). We were unable to characterize the relationship between mucus hypersecretion and sputum purulence (p. 116).

Causes of chronic mucus hypersecretion

By far the most important cause of chronic mucus expectoration is smoking, particularly of cigarettes. In virtually all prevalence studies, the proportion of subjects who admit to regular phlegm production is linearly related to current smoking habits. The proportion of ex-smokers affected is much less than that of continuing smokers (Table 6.8, p. 118), although still greater than that of non-smokers. In our study, smoking habits are highly correlated with both phlegm score and sputum probit. Mucus expectoration is usually reduced when smoking stops (Wynder *et al.* 1965), and we found that it declined significantly in men who reduced their cigarette smoking. Expectoration is quite strongly correlated with airflow obstruction, and we have already given our reasons for considering this to be due to the existence of a special susceptibility that some individuals have to expectoration and to more rapid loss of FEV.

Among the non-smokers at the initial survey, about one in seven returned a non-empty sputum bottle (Table 3.14, p. 47). A comparison of these non-smokers with sputum with a sample of smokers matched for age and sputum volume showed a significantly higher incidence of childhood bronchitis in the non-smokers (Fletcher 1965). It is possible that some men eschew smoking because they already have a productive cough in adolescence, when most smokers adopt the habit, and continue to have this symptom as adults. That air pollution is a cause of expectoration as well as of airflow obstruction is suggested by the increased proportion of people living in polluted areas who report phlegm production compared with the proportion in country dwellers (Holland and Reid 1965). Other, unknown factors may also increase the prevalence of expectoration, as is shown in Britain by its increased frequency in both adults and children in the lower compared with the higher social classes (College of General Practitioners 1961; Colley and Reid 1970).

The natural history of chronic obstructive lung disease

Our study has enabled us to describe the development of potentially disabling airflow obstruction only as we have observed it in adult men using the FEV as a test of impairment of expiratory airflow. Our observations, together with the findings of many other epidemiological studies, indicate that mucus hypersecretion, bronchial infec-

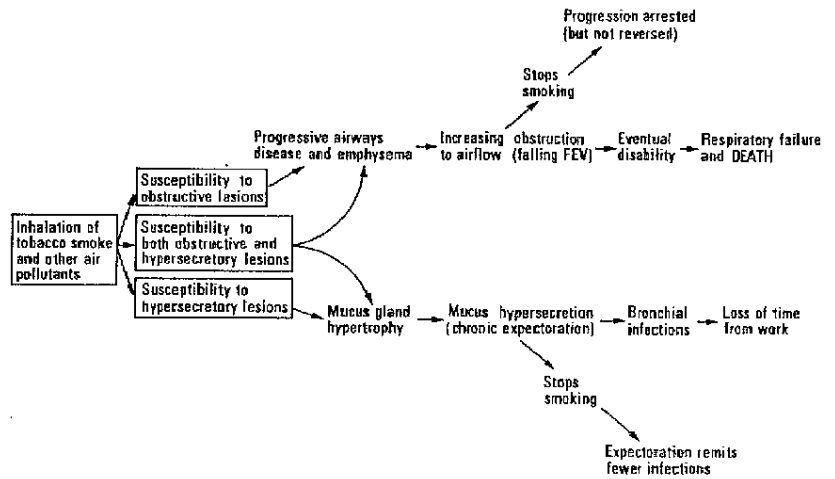


Fig. 7.2. The distinct natural histories of the obstructive and hypersecretory disorders

'Other air pollutants' may be general, or occupational.

tion, and airflow obstruction, which have been widely regarded as components of a single disease ('chronic obstructive bronchitis'), consist in fact of two largely distinct processes, caused by two linked susceptibilities to smoking and other forms of air pollution (Fig. 7.2). On the one hand, there is mucus hypersecretion, which increases liability to persistent or recurrent bronchial infection and, on the other, there is the more sinister development of airflow obstruction. The latter is itself a complex disorder due in varying proportions to small airways disease and to various forms of emphysema. In describing the development of chronic obstructive lung disease, as we have observed it in adult men, we must consider the hypersecretory disorder and the obstructive disorder separately.

The hypersecretory disorder consists of hypersecretion of bronchial mucus, derived from enlarged bronchial mucus glands and also, to a much lesser extent, from hyperplastic goblet cells, causing a productive cough. It is itself a reaction, in susceptible individuals, to smoking and to other forms of generalized and industrial air pollution. Its severity increases with increasing degrees of exposure to causative irritants, being, for instance, greater in heavier than in lighter smokers. It is not clear whether its severity increases with increased duration of exposure. In most surveys, it has been found to be more prevalent and severe in older than in younger subjects, but in others no such increase has been found (Higgins 1974). In our own initial survey

there was only a small increase with age (Table 4.6, p. 67). It decreases when exposure to the causative irritant stops—as in ex-smokers or in migrants from the polluted towns of the United Kingdom to less polluted areas of the United States (Reid 1971).

The only disability mucus hypersecretion causes, in the absence of severe obstructive disease, is an increased liability to bronchial infections which result in recurrent illnesses and absence from work. In subjects with severe obstruction, however, such infections often precipitate respiratory failure which may be fatal.

The obstructive disorder is due, in varying proportions, to disease of the airways and to emphysema. Using the simple test of FEV, we have been able to study the natural history of this disorder only when it is severe or extensive enough for maximum expiratory airflow to become significantly limited by these conditions. Its main cause today is cigarette smoking, but general and industrial air pollution are contributory causes (Bennett *et al.* 1972).

Only a small proportion of cigarette smokers and of those exposed to other pollutants develop airflow obstruction to a degree which may be disabling, this proportion being greater in heavier smokers. In these individuals, it usually develops gradually without sudden worsening (Appendixes, sections B.9, B.11, and Appendix C). The proportion of significantly affected smokers increases with age. This finding is consistent with the rarity of significant emphysema in autopsy studies before the age of 40 and with the increasing proportion so affected with increasing age thereafter (Anderson *et al.* 1972; Auerbach *et al.* 1972; Thurlbeck *et al.* 1974). We find that the rate of loss of FEV accelerates slowly with advancing age (Appendixes, section B.9). Although the overall rate of loss is fairly regular, it may increase or decrease over periods of years. It appears that in some people, decline may accelerate rather rapidly after a period of slow advance. This might be expected if a steady rate of damage to the small airways is occurring throughout life without any great effect on the FEV until small-airways resistance and loss of elastic recoil are severe enough to increase total resistance to airflow significantly. Rapid decline of FEV usually reverts to a normal rate of decline if smoking is stopped, but it may also slow down for no apparent reason even in some patients with severe obstruction; patients with substantial FEV loss sometimes continue without much further deterioration for several years.

We know almost nothing about the factors that determine which individuals will and which will not react to tobacco smoke and other air pollutants by developing either or both of the hypersecretory and obstructive disorders. There is fairly good evidence that familial

factors may play a part (Oswald *et al.* 1953; Layland 1964; Cederlof *et al.* 1967; Larson *et al.* 1970). Severe deficiency of α_1-antitrypsin certainly causes a high degree of susceptibility (Erikson 1965) but is too rare an abnormality in the homozygous state to account for more than a minority of cases of emphysema. Although some studies of relatives of patients with this deficiency have suggested that heterozygotes with minor deficiencies may have a greater liability to the disease (Mittman *et al.* 1971), no such tendency has been found in complete population studies (Morse *et al.* 1975). There is little evidence to suggest that heterozygotes for the commoner abnormality of cystic fibrosis have any special liability to chronic obstructive lung disease (Muir *et al.* 1962; Hallet *et al.* 1967). No differences have been found between the distribution of blood-groups in bronchitic patients and the general population (Stuart-Harris 1965).

The role of allergy in the causation of chronic airflow obstruction is controversial, largely owing to difficulties of differentiating persistent asthma from chronic obstructive lung disease (Kreukniet and Young 1964; Charpin *et al.* 1964; Ciba Guest Symposium 1971). We have found that allergy, as assessed by questionnaires about eczema, urticaria, hay fever, or migraine, is irrelevant to the obstructive disorder; that sputum eosinophilia might be weakly related to it; but that clinically asthmatic subjects do appear to suffer appreciably more rapid FEV loss. However although this last finding, if confirmed in a larger series of asthmatic patients, may be of considerable relevance to certain asthmatic individuals, it is not of much relevance to the overall natural history of the obstructive disorder, since the great majority of obstructed individuals are not asthmatic, in the sense of having reversible airflow obstruction.

Terminology

Recognition of the distinction between the hypersecretory and obstructive disorders requires revision of current terminology, particularly with regard to the common use of the term 'chronic bronchitis' to describe both or either of these disorders without any regard to this distinction.

If this term had been used only to indicate expectoration, its meaning would have remained clear, but it has come to be used to describe various symptomatic and clinical syndromes, and its meaning has become increasingly ambiguous (World Health Organisation 1975). We suggest that it should be used much less widely, and that in its place the different components which have been regarded as contributing to 'bronchitis' to varying extents should be specifically

named in any publication or discussion of them (e.g. mucus hypersecretion (or 'bronchial catarrh', to revert to Laennec's simple terminology); bronchial infection; and irreversible airflow obstruction—or its components, intrinsic airways disease and emphysema). There may be occasions when it will be convenient to use the omnibus term 'chronic obstructive lung disease' or, when asthma is to be included, 'chronic non-specific lung disease' (Ciba Guest Symposium 1959). It is particularly important that the distinct pathogenesis of the hypersecretory and obstructive disorders should be kept in mind when talking or writing about what has hitherto been regarded as a single disease under the comprehensive term, chronic bronchitis.

Identification of early chronic obstructive lung disease in order to prevent its development

In recent years, it has often been proposed that, since only a minority of smokers or of those exposed to general or occupational air pollution develop disabling airflow obstruction, disability might be prevented if these susceptible subjects could be identified at an early age. They might then be dissuaded from starting to smoke, or, if already smoking, be given special assistance in stopping, and advised to avoid exposure to other harmful forms of air pollution. We shall not consider here the special case of homozygotes for α_1-antitrypsin deficiency, who certainly need protection because of their very high risk, but shall discuss how the majority of susceptibles with no such recognizable characteristics might be identified. Identification may be considered within three broad age groups.

In childhood

In Britain it has been shown that children who develop lower respiratory tract infection, who live in polluted areas or who belong to the 'lower' social classes have an increased liability to develop productive cough and have worse lung function in childhood, as shown by measurements of peak expiratory flow rate (Holland *et al.* 1969*a*, *b*; Reid 1969, 1970). It has consequently been suggested that these children will later have an increased liability to develop chronic obstructive lung disease. This is an attractive hypothesis but is no more than this, for it has not yet been substantiated, and cannot be until such children have been followed at least until the fourth decade of their lives when unequivocal evidence of chronic obstructive lung disease may first be obtained.

It has been shown, in one group of children followed into their

third decade, that the prevalence of bronchial catarrh is greater in those who are known to have had a lower respiratory tract infection in infancy (Colley *et al.* 1973). It has also been found that soldiers who have spent their childhood in polluted areas in England and Wales have a higher incidence of 'respiratory disease' during their service than those who came from less polluted areas (Rosenbaum 1961) but, of course, these young adults would not yet be of an age when they could have developed significant irreversible airflow obstruction.

If our conclusion that the hypersecretory and obstructive disorders are largely independent, apart from a common susceptibility to both, is correct, identification in childhood based chiefly on bronchial catarrh or bronchial infection may help identify the more susceptible subjects. But on the other hand it may, despite the correlation between the two conditions, be no more relevant to the development of chronic obstructive lung disease than these conditions are in middle age.

In early adult life

Smokers do, on average, have slightly lower values of FEV than non-smokers (Ashford *et al.* 1961; Peters and Ferris 1967).† Some young adult smokers with normal values on simple tests like the FEV, however, show abnormalities on 'sensitive tests', which are not unreasonably assumed to indicate some sort of small airways disease. It has naturally been suggested that these tests could be used to identify susceptibles before any severe irreversible airflow obstruction had developed (Macklem 1972; Bates 1974). As in the identification of susceptible children, this hypothesis has not yet been tested by the 15–20 year follow-up which would be needed to establish its validity. But abnormal closing volumes are often found in middle-aged smokers who have retained normal FEV levels (McCarthy *et al.* 1972). Our evidence suggests that such smokers are most unlikely to develop severe airflow obstruction. An abnormal closing volume can thus be irrelevant to prognosis in middle age, and if irrelevant in middle age it may not be relevant at earlier ages.

In middle age

Our findings suggest that many susceptible smokers could be identified during middle age by their having developed a significant

† The apparent conflicting observation of Ferris *et al.* (1965) that linear regressions of FEV on age in smokers and non-smokers cross over at the age of 30, so that at earlier ages smokers appear to have higher FEV levels, is presumably an artefact due to fitting linear regressions to a rate of decline with age which is actually curvilinear (see Fig. 3.2, p. 45).

reduction of FEV level. These smokers would already have developed a considerable degree of chronic airflow obstruction, and this trend towards serious disability is likely to continue unless they stop smoking. If they do this, their accelerated FEV decline is likely to revert to a normal rate of decline, and progression to disablement may be delayed or avoided (Fig. 7.1, p. 130). As the degree of small airways disease already present by middle age in susceptible smokers must be very considerable, new, specific tests may be forthcoming which will detect these changes with greater sensitivity, and thus earlier, than can be achieved by simple spirometry. (It is incorrect to argue, as do Krumholz and Medrick (1973), that 'FEV is of no use as a screening test in middle age because mean FEV among smokers, although lower than the mean among non-smokers, is still within normal limits.')

It is, however, difficult to use a simple test like the FEV for individual diagnosis. What is needed is to discover how much FEV a middle-aged smoker has lost owing to his smoking. For this we need to know both his FEV now and what it should have been had he never smoked—the 'expected FEV'. To determine his FEV now may need a few measurements over a period of a month or so to see the best that he can do. The expected FEV cannot be known accurately for there is such a wide range of normal values (2 S.D. = ± 1 litre) even after allowing for age and height. The best that can be done for the present is to accept that a middle-aged smoker whose FEV is 1 litre below the expected value is very likely eventually to become disabled by low FEV unless he stops smoking. This is probably as accurate a method of assessing prognosis as is available in many other fields of medicine. An ideal method by which the prediction might be improved would be if means could be found to ensure that most people had an accurate forced expiratory spirometric trace recorded in early adult life and to arrange that the records could be readily retrieved. At present this proposal hardly seems practicable.

Summary of conclusions

We have observed two largely distinct chronic disorders of structure and function of the lung (see Fig. 7.2, p. 141), the obstructive disorder (intrinsic airways disease and/or emphysema causing impairment of expiratory airflow with eventual disability), and the hypersecretory disorder (increased activity of mucus-secreting glands causing expectoration with increasing liability to clinical bronchial infections). Both are caused predominantly by smoking (particularly of cigarettes), with other forms of air pollution playing a contributory

role. Because of this common cause and because they develop only in subjects with constitutional susceptibilities which are often linked with each other, they commonly occur together, but they may develop independently of each other, particularly in their early stages. Our study of an employed population cannot tell us whether, when the obstructive disease is advanced, it may itself promote an increase of hypersecretion and infection.

Mucus hypersecretion, chiefly derived from the larger airways, develops fairly rapidly in response to smoking and often remains constant over many years. It usually remits when exposure to smoking and air pollution ceases and it both predisposes to and is a temporary effect of bronchial infection.

The obstructive disorder appears to be distinct from asthma as diagnosed clinically, is much commoner than asthma, and is largely irreversible. It develops gradually over decades only in susceptible subjects who smoke or who are exposed to heavy air pollution or industrial dusts or fumes with a consequent gradually accelerating reduction in values of simple spirometric tests of expiratory airflow such as the FEV. This reduction permits detection in middle age of subjects who are likely to progress to severe disablement. It seldom causes disability before the age of 50 except in very high-risk subjects such as those with α_1-antitrypsin deficiency. If susceptible subjects stop smoking, the rate of subsequent FEV loss is much less rapid than if smoking had continued, so that disability may be delayed or averted. Since the rate of loss of ventilatory capacity in susceptible subjects is determined by their degree of susceptibility and, given this, is unaffected by mucus hypersecretion or by bronchial infection, neither of these are of any sinister prognostic significance in middle-aged subjects in the absence of airflow obstruction. The main constitutional factors which determine susceptibility to either (or both of) the hypersecretory or obstructive disorders are not known, but they are familial (Layland 1964; Larson *et al.* 1970) and so they could be partly inherited.

In view of the independence of the hypersecretory and obstructive disorders, it is inappropriate to refer to either or both of them by the term 'chronic bronchitis'. This term should no longer be used without qualification unless the context is such as to make the intended meaning clear.

Suggestions for future research

Although we are confident of our conclusion that the two disorders are not as strongly linked as was previously supposed, it is desirable

that this conclusion should receive independent confirmation. More complete analysis of prevalence studies could be useful. In such studies, the relationships between mucus hypersecretion, infection, and airflow obstruction have usually been demonstrated merely by looking at mean FEV values in various groups of subjects. FEV levels in middle age are correlated with FEV slopes, so that FEV levels themselves provide a useful index of the rate of progression to airflow obstruction. Re-analysis of much existing data should at least provide confirmation or refutation of our finding that a large proportion of subjects with mucus hypersecretion and a history of recurrent infections have normal levels of FEV and that a considerable proportion of subjects with reduced FEV have no evidence of mucus hypersecretion or recurrent infection. It will not be easy to confirm our finding of little relationship between FEV levels and chest infections, given mucus hypersecretion, in prevalence studies, for chronic mucus hypersecretion cannot be assessed sufficiently accurately for that purpose by a single measurement.

Our group of 'obstructed' ex-smokers was so small that although we are confident that they derived some benefit from stopping smoking, we are unable to quantify the benefit accurately. Further studies are needed of the changes of FEV that occur in obstructed smokers when they stop smoking, at various ages and with various degrees of mild obstruction.† This would require several measurements of levels of FEV (or similar tests) initially, followed by another set of such measurements more than five years later to provide a reasonably accurate measure of rate of decline. This should be done both in obstructed smokers who do and in those who do not stop smoking. Studies of the effect of stopping on subsequent FEV decline would be of less interest in middle-aged smokers without airflow obstruction because, not being very susceptible to the obstructive disorder, their rates of decline of FEV will be almost unaffected by stopping smoking.

Such investigations could also be combined with further studies of the key problem in prevention, which is how to persuade smokers to stop. How far, for instance, can repeated lung function measurements—perhaps using special 'sensitive' tests—be used to increase and maintain determination to stop by demonstrating benefit in those who stop compared with lack of benefit in those who do not? At the same time, obstructed smokers who could or would not stop should be persuaded to use modified forms of cigarettes (e.g. with low tar levels or containing 'new smoking materials') to see whether this

†There are, of course, plenty of 'obstructed' ex-smokers in clinical series, but nearly all of these will be men who did not stop smoking until they were already disabled.

lessens the rate of decline of ventilatory capacity compared with those who continue to smoke ordinary cigarettes. Although primary prevention of smoking-related diseases is needed by universal discouragement of smoking, modified forms of smoking which may be less hazardous also need to be developed and monitored, to see what effects they have on those who do start to smoke and become addicted to it.

Another requirement is that better means of early detection of susceptible individuals should be developed. A simple test like the FEV can be used, as we have used it, to study group differences in levels and rates of change of preclinical airflow obstruction, but it is unsatisfactory for individual diagnosis because of the wide range of 'normal' values. This range might be reduced by using more refined methods of predicting individual expected values. Any such development would be of immediate prognostic value because lowered values of simple tests of expiratory airflow are necessarily of some value as predictors of development of clinical airflow obstruction. But other, more specific, tests, suitable for field use, would be useful, especially if they could distinguish between small airways disease and the various types of emphysema and thus permit a more complete study of the natural history of different aspects of the obstructive syndrome than we have been able to make. Long-term follow-up studies of subjects who have already been studied by the various 'sensitive' tests of small airways disease are required to see how well such tests detect those who will later develop significant airflow obstruction. The likelihood that any test will turn out to be a good predictor could be studied in a preliminary way simply by looking at its correlation with tests such as the FEV in middle-aged smokers. Any test which does not correlate reasonably with the FEV in middle-aged smokers is unlikely to have much prognostic significance.

The weakness of mucus hypersecretion as a predictor of future disability makes it a far less valuable screening measurement than almost any spirometric measurement would be. Population (or industrial) screening programmes should never be based solely on the results of questionnaires, and it is desirable that permanent traces of all spirometric tests be generated.

Lastly, there is the central question of why some smokers do and others do not develop airflow obstruction. The only clues we have are that the determinants of susceptibility to more rapid loss of FEV are correlated with the determinants of expectoration, that they do not vary within one individual as the amount of expectoration varies, and that since many individuals develop one disorder without the other, the determinants are unlikely to be identical. The first requirement is

to develop hypotheses about the nature of these determinants. They could then be tested in simple cross-sectional surveys of people who have smoked regularly until middle age. The 15 per cent of middle-aged lifelong smokers with the highest levels of FEV (standardized for age and height) could be used as '*non-susceptible controls*' for comparison with the 15 per cent with the lowest FEV levels (after confirmatory measurements to ensure that the low levels were genuine), without any selection in either group for the presence or absence of hypersecretion. Such case-control studies could be used to test any factor that might be thought to indicate susceptibility to the obstructive disorder. It is also desirable that in all cross-sectional studies of chronic obstructive lung disease, serum samples (at least from such contrasting groups as the top and bottom 15 per cent (by FEV) of middle-aged lifelong smokers) should be taken and stored to facilitate future assays of any serum factor which might be suggested to be relevant to susceptibility.

If the basis for this susceptibility could be established, our understanding of the mechanisms whereby the obstructive, and perhaps the hypersecretory, disorders develop will be increased. This might well lead to more practical preventive strategies and to therapeutic techniques which are not, as at present, entirely palliative.